# EXHIBIT C13

**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF NEW JERSEY**

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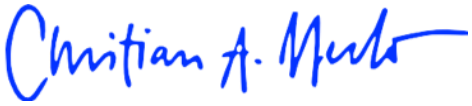
| **IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION**<br><br>***THIS DOCUMENT RELATES TO ALL CASES*** | **MDL NO. 16-2738 (FLW) (LHG)** |

# EXPERT REPORT OF CHRISTIAN MERLO, MD, MPH FOR GENERAL CAUSATION *DAUBERT* HEARING

Date: February 25, 2019



Christian Merlo, M.D., M.P.H.

## I. SCOPE OF REPORT

I was asked to address fundamental tenets of epidemiology, to review the epidemiology related to the potential association between perineal talc use and ovarian cancer, to review plaintiffs' epidemiology experts' reports, and to offer my opinions on their methodologies.

All of the opinions in this report are stated to a reasonable degree of scientific certainty.

I am being compensated at a rate of $530 per hour for record review and drafting my report and $720 per hour for testimony.

My curriculum vitae, a list of literature that I have reviewed, and a list of testimony I have provided in the last four years may be found in Appendices A, B and C.

## II. PROFESSIONAL QUALIFICATIONS

My name is Christian Merlo. I am a licensed physician in the state of Maryland and am board certified in internal medicine, pulmonary medicine and critical care medicine. I am an attending physician at the Johns Hopkins Hospital and the Johns Hopkins Bayview Medical Center and care for patients both in the hospital and in our outpatient centers. I am Associate Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at the Johns Hopkins University School of Medicine, and in addition, I am Associate Professor of Epidemiology in the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health. I am also a member of the *Alpha Omega Alpha* honor society for medicine.

I have provided patient care and consultation as a clinical physician and have taught medicine in the fields of general medicine, pulmonary medicine and critical care medicine for more than 18 years.

I received my doctorate in medicine at Georgetown University School of Medicine and completed my residency in internal medicine at Georgetown University Medical Center, where I also served as Chief Resident. I completed a four-year fellowship in Pulmonary and Critical Care Medicine at the Johns Hopkins Hospital, and during this period in time, I also received a master's degree in public health from the Johns Hopkins Bloomberg School of Public Health.

I was offered a faculty position in 2004 as Instructor in Medicine at the Johns Hopkins University School of Medicine, and was promoted to Assistant Professor of Medicine in 2006. In 2009, I was awarded a joint faculty appointment as Assistant Professor of Epidemiology at the Johns Hopkins Bloomberg School of Public Health, and in 2015, I was promoted to Associate Professor of Medicine and Epidemiology.

I am the Associate Program Director of the Adult Cystic Fibrosis Program at the Johns Hopkins Cystic Fibrosis Center, one of the largest cystic fibrosis centers in the country, and in addition, I am the Director of Research for both the Adult Cystic Fibrosis Program and the Lung Transplant Program at the Johns Hopkins Hospital. I am also an Associate Program Director for Research and Scholarship for the Osler Medical Residency

program. I have specific expertise in the clinical care of patients with cystic fibrosis and those who undergo lung transplantation, as well as in the care of patients with other pulmonary diseases or those that require critical care therapies. My research involves the design of clinical studies investigating the impact of environmental and infectious exposures on outcomes for patients with cystic fibrosis and those who undergo lung transplantation.

I am currently principal investigator or co-investigator on many NIH-funded and pharmaceutical industry-sponsored clinical trials. I have authored or co-authored more than 70 manuscripts, book chapters and commentaries on topics involving cystic fibrosis and lung transplantation, as well as on topics in general pulmonary medicine and critical care medicine. As a clinical investigator, I have had rigorous training and have expertise in clinical epidemiology, with specific training in clinical trial design, conduct and analysis. My ties with the School of Public Health have provided ongoing collaboration to help research the epidemiologic nature of the exposure/outcome causal pathway in diseases involving internal medicine, pulmonary medicine and critical care medicine.

I am also an expert in the methodologic approach to the study of disease and have more than 15 years of experience teaching coursework on study design and analysis, as well as conducting research on the epidemiologic nature of the exposure/outcome relationship with a strong command of the strengths and limitations of epidemiologic investigation.

## III. FUNDAMENTAL PRINCIPLES OF EPIDEMIOLOGY

Although there are many definitions of epidemiology, a widely accepted definition describes epidemiology as:

> *the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems.*[1]

Epidemiology is a scientific discipline that relies heavily on an unbiased approach to the collection, analysis and interpretation of data. Epidemiology places an emphasis on the frequency and rate of health events as well as how personal characteristics such as demographics, socioeconomic status, behaviors and environmental exposures play a role in health-related events. Epidemiology is a science, and epidemiologic studies, when designed, conducted, analyzed and interpreted appropriately, can be powerful tools in the critical examination of the causal pathway between exposure and outcome.

### *A. Fundamentals Of Epidemiologic Study Design*

Researchers often have to choose a study design based on the research question, as not all study designs are appropriate for all questions. Many research questions are suitable to be answered using a classic experimental design such as the randomized controlled trial. For instance, it may be appropriate to use a randomized controlled trial design to investigate

[1] *See, e.g.*, Centers for Disease Control & Prevention, Principles of Epidemiology in Public Health Practice, Third Edition, An Introduction to Applied Epidemiology and Biostatistics, Lesson 1: Introduction to Epidemiology, https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section1.html (footnote omitted).

the effect of a new cholesterol lowering agent on mortality in patients with heart disease. An example of this is the Scandinavian Simvastatin Survival Study,[2] in which researchers studied 4,444 patients with heart disease who were either treated with simvastatin or placebo. The investigators found a significant reduction in the risk of death from heart disease in the simvastatin group compared to placebo.

Other research questions are not suitable for an experimental design in humans because of the potential for harm, lack of equipoise or ethical concerns. One such example is the effect of cigarette smoking on risk of death and risk of death from lung cancer. In order to attempt to answer this, researchers would not be able to use an experimental design, and more likely would have to use an observational study design. Doll and Hill[3] sent out a short but detailed questionnaire asking more than 59,000 British physicians about smoking habits and obtained follow-up information regarding mortality and lung cancer risk. In this very large observation cohort, Doll and Hill were able to demonstrate a significant increase in all-cause mortality as well as deaths due to lung cancer among cigarette smokers when compared to non-smokers.

Sometimes, the experimental study design is appropriate, and other times, an observational study design is necessary, but it is only with careful and detailed attention to the study design (study type, study size, exposure assessment, attempt to limit bias and confounding), conduct and analysis that the cause of disease can possibly be determined.

### *B. Limitations Of Epidemiologic Study Design*

All epidemiologic studies have the advantage and limitation of studying humans rather than experimental animals. Each epidemiologic study design (detailed in the **STUDY DESIGN CONSIDERATIONS** section), however, not only has its strengths, but also weaknesses.

For example, consider the design of an epidemiologic study to evaluate the question:

*"Does regular aerobic exercise decrease the risk of heart disease?"*

A randomized controlled trial, one might think, would be the most rigorous approach and the method most similar to a laboratory scientist working in a highly controlled environment with experimental animals. Suppose researchers choose a group of subjects who don't exercise regularly, divide the group randomly into an intervention group, who are instructed to perform aerobic exercise for 30 minutes three times a week, and a control group, who are instructed to continue with a low exercise lifestyle. The investigators will follow both groups looking for signs of heart disease, and if they are correct, subjects who exercise will get less heart disease. With this study design there may be a problem with controlling how much the subjects exercise. In the laboratory, a scientist can control exactly how much an experimental animal exercises, but in the real world this

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[2] The Scandinavian Simvastatin Survival Study Group, *Design and baseline results of the Scandinavian Simvastatin Survival Study of patients with stable angina and/or previous myocardial infarction.* (1993) 71 Am J Cardiol 393.

[3] Doll & Hill, *The mortality of doctors in relation to their smoking habits*. (1954) 328 (7455) BMJ. 1529 .

may be difficult to control. The intervention group may become lazy and not exercise, while the control group might have concern about heart disease and increase exercise, which would affect the study results.

The researchers might attempt a cohort study and follow a large group of people without heart disease over a period of time and ask them detailed questions about exercise and then after several years compare the rate of heart disease among those who exercise regularly to those who do not. Again, if the researchers are correct, patients who exercise regularly will develop less heart disease. One potential problem with this design is that people who exercise regularly may differ in other ways from people who do not exercise regularly. For example, the people who exercise regularly might be more likely to eat healthier and less likely to smoke and have a reduced risk of heart disease that is unrelated to exercise.

The researchers might also choose to perform a case-control study and identify a group of people with heart disease from the hospital coronary care unit as well as a comparable group from the hospital without heart disease. The investigators would then question both groups about their exercise over the past several years and classify each as either exercising regularly or not exercising regularly. Once again, if the researchers are correct, the patients with heart disease will report less exercise than controls. One potential problem with this approach is that people may not be able to remember their exercise patterns, or those with heart disease might feel self-conscious about reporting true exercise patterns and the information obtained about the exposure may not be reliable.

## IV. EVALUATING THE ACCURACY OF EPIDEMIOLOGIC STUDIES

### *A. Accuracy Of An Epidemiologic Study*

In an ideal setting, all epidemiologic studies would be designed, conducted, analyzed, and interpreted in a fashion that eliminated sources of error. One of the major goals for epidemiologists is to minimize error as much as possible. Similarly, it is important for those who read and use the epidemiologic literature to be cautious in how the information is interpreted. As such, it is important to understand the factors that can influence the accuracy of epidemiologic study as errors can arise from three main sources – bias, confounding and random error.

Accuracy requires both validity and precision. Bias and confounding affect the validity of a study, while random error affects the precision of a study.

### *B. Validity*

Validity of epidemiologic studies is defined as the "degree to which inferences are warranted given the methods and study population chosen."[4] There are two major types of validity – internal validity and external validity. Internal validity represents how well the study findings, aside from random error, represent the truth in the population being studied. The internal validity of an epidemiologic study can be challenged by systematic error caused by either or both of bias and confounding. This systematic error in the study design, conduct, analysis or interpretation can lead to either artificial elevation or artificial

[4] Oleckno, *Epidemiology: Concepts & Methods* (2008).

reduction in the measures of association between exposure and outcome. External validity, sometimes referred to as generalizability, is the extent to which the results of the study can be applied to populations other than the population under investigation. It is often felt that internal validity is more important than external validity because if a study is not valid, then why would one generalize a non-internally-valid study to another population. The above-mentioned Scandinavian Simvastatin Survival Study[5] results were believed to be internally valid, and it was also felt to be reasonable to apply these results to other populations.[6]

### *C. Bias*

Bias is a type of systematic non-random error in the design and/or conduct of an epidemiologic study. Bias can have a dramatic effect on the internal validity of a study and because of this, can affect the accuracy of the study. In general, bias can be broken down into two main categories, known as selection bias and information bias. Both of these types of bias can lead to either an overestimation or underestimation of risk in epidemiologic studies. Although bias can be present in all types of studies, bias can be a particularly significant concern in observational studies, especially in those studies that are poorly designed.

Selection bias refers to a systematic error due to the way in which subjects are selected for the study. This type of bias can occur when the subjects in the study population differ from the subjects in the source population. This can occur in a cross-sectional or case-control study when the frequency of the exposure or outcome differs systematically between the study population and the source population. Because of this, selection bias can sometimes lead to an association when one does not actually exist. For instance, an investigator interested in researching whether coffee drinking is associated with a specific type of cancer designs a case-control study and obtains cases from an oncology clinic. The investigator obtains controls from a nearby heartburn clinic. The study is performed, and the investigator finds that coffee drinkers are 1.5 times more likely to develop a specific type of cancer. Since controls are recruited from a different clinic than the cases, it is possible that controls may be systematically different from cases in a way that may affect the study results. In fact, since controls were recruited from a nearby heartburn clinic where patients are routinely instructed to reduce or stop coffee drinking, controls are less likely to be coffee drinkers than all people who would be eligible controls and lead to an overestimate of risk due to selection bias.

Information bias refers to a systematic error due to measurement errors that leads to misclassification of study subjects with regards to either exposure or outcome. Information bias tends to occur during the data collection portion of an epidemiologic study. This misclassification of either exposure or outcome can be characterized as either differential or nondifferential. Differential misclassification can occur when the likelihood of misclassification is different between the study and comparison groups. Differential misclassification may lead to either overestimation or underestimation of the true value of the measure of association. If the cases in a case-control study are more likely to be

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[5] The Scandinavian Simvastatin Survival Study Group. *Design and baseline results of the Scandinavian Simvastatin Survival Study of patients with stable angina and/or previous myocardial infarction.* (1993) 71 Am J Cardiol 393.

[6] *Id.*

misclassified as exposed than the controls, then the study will tend to overestimate the true estimate of risk (odds ratio).

For example, suppose an investigator is interested in studying whether high blood pressure is associated with drinking sugary drinks. A case-control study is designed, and the investigator finds 200 cases with high blood pressure and 200 controls with normal blood pressure. The investigator then asks questions about sugary drink habits during the previous five years. The responses are collected and analyzed (table a), and there is a statistically significant increase in risk of high blood pressure with drinking sugary drinks (OR: 3.67; p<0.001), suggesting sugary drinks are associated with high blood pressure. If cases are systematically more likely to report sugary drink usage than controls (differential misclassification because of the belief that sugary drinks may cause high blood pressure), then this will lead to an overestimation of the true estimate of risk. In reality, if there was no increase (table b) in reporting sugary drink consumption among cases (no misclassification), there would be a non-statistically significant estimate of risk (OR: 1.35; p=0.13).

a.

| | Study | | | |
|---|---|---|---|---|
| | High BP | No high BP | | |
| Sugary drinks | 150 | 90 | OR=3.67 | P<0.001 |
| No sugary drinks | 50 | 110 | | |
| | 200 | 200 | | |

b.

| | Truth | | | |
|---|---|---|---|---|
| | High BP | No high BP | | |
| Sugary drinks | 105 | 90 | OR=1.35 | P=0.13 |
| No sugary drinks | 95 | 110 | | |
| | 200 | 200 | | |

Nondifferential misclassification can occur when there is likely an equal proportion of misclassification of exposure status among those with and without an outcome or of outcome status among those with and without an exposure. This type of misclassification typically results in a dilution of the effect of exposure on outcome and is more likely to result in no association when an association between exposure and outcome actually exists.

One specific type of bias that leads to misclassification and that is common in case-control studies is known as recall bias. It often results from the fact that cases tend to remember past exposures more than controls. It may also arise if cases are more likely than controls to investigate whether certain risk factors increase the risk of developing a certain disease. Recall bias is often less likely to occur when both cases and controls are patients, for example, in hospitalized patients,[7] where the degree of thinking about a possible exposure or outcome is likely to be at similar levels. Consider again the above example of the investigator who is trying to determine if there is a relationship between sugary drinks and high blood pressure. If the cases tend to recall and report more sugary drink consumption simply because they have reflected more on their past experiences, recall bias

[7] Schultz & Grimes, *Case-control studies: research in reverse*. (2002) 359(9304) Lancet 431; Schlesselman, *Case-control studies: design, conduct, analysis* (1982).

could result in an overestimation of the measure of risk between the sugary drinks and high blood pressure.

As particularly pertinent here, in one case-control study involving the potential association between perineal talc use and ovarian cancer,[8] the investigators examined whether cases and controls reported talc use more frequently if they were interviewed after 2014, which is the year when two widely publicized lawsuits concerning talc use were filed, as opposed to before that year. For those interviewed prior to 2014, approximately the same percentage of cases and controls reported genital talc use (36.5% for cases, 34.0% for controls). For those interviewed after 2014, cases reported talc use 51.5% of the time, while the percentage of controls reporting talc use remained about the same (34.4%). This is a clear demonstration of the effect of recall bias in case-control studies. Critically, that study found a statistically significant risk of ovarian cancer for those who were interviewed after 2014 at 2.91 (95% CI: 1.70-4.97). For those interviewed prior to 2014, no statistically significant association was found.[9] As discussed in Section VIII.B below, such concerns of recall bias could have affected pre-2014 studies as well.

Selection and information bias can best be controlled and prevented during the design and conduct of a study. This means that investigators must recognize the potential sources of bias and take precautions to minimize this bias. Methods have been developed to prevent or minimize bias in epidemiologic studies. Some of these include attempts to standardize data collection, pilot test data collection instruments, use objective methods to measure exposure and outcome status, verify subject response from other sources and obtain multiple measurements of exposure and outcome status.

### *D. Confounding*

In epidemiology, confounding is a misrepresentation of the true effect of an exposure on an outcome due to an association between the exposure and another factor. This factor is often referred to as a confounder, and like bias, confounding is a systematic, non-random error that can affect the internal validity of a study. Confounding can result in an overestimation or underestimation of the true effect of an exposure on an outcome. In general, for another factor to confound the effect of an exposure on the outcome, three conditions must be met: (1) the factor must be associated with the exposure; (2) the factor must be associated with the outcome; and (3) the factor must not represent a step in the causal pathway between exposure and outcome. Many times, epidemiologists do not know what extra factors will confound an actual effect of an exposure on an outcome, but it is important for suspected factors to be considered as potential confounders. Experienced epidemiologists are usually able to anticipate suspected confounders given previous experience in similar studies or based on previous studies looking at a similar exposure outcome relationship.

The Sister Study, which I discuss in more detail below, is one example of potential confounding affecting the measurement of the effect of genital talc exposure.[10] In that

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[8] Schildkraut et al., *Association between Body Powder Use and Ovarian Cancer: The African American Caner Epidemiology Study (AACES)*. (2016) 25(10) Cancer Epidemiol Biomarkers Prev. 1411.

[9] *Id*.

[10] Gonzalez et al., *Douching, Talc Use, and Risk of Ovarian Cancer*. (2016) 27 Epidemiology 797.

study, in addition to talc use, participants were also asked about their douching habits. Of the 50,884 women who completed questionnaires, 154 women developed ovarian cancer. Ever douching during the 12 months prior to the study was associated with a statistically significant risk of ovarian cancer (HR: 1.8; 95% CI: 1.2-2.8) when compared with never douching after adjusting for confounders.[11] In contrast, there was no statistically significant increase risk of ovarian cancer (HR: 0.73; 95% CI: 0.44-1.2) with ever talc use during the 12 months prior to the study when compared with never talc use after adjusting for confounders.[12] There was no change in the estimated effect of talc use after adjustment for douching, and similarly, there was no change in the estimated effect of douching after adjusting for talc use. If those who use talc are more likely to douche, as is demonstrated in this and other studies,[13] and douching has a significant effect on the risk of ovarian cancer in this study, prior studies that have revealed a significant effect of talc on ovarian cancer may have been confounded by douching.

Although the amount of confounding is the degree to which the measure of association is affected, it is not appropriate to evaluate confounding using statistical tests of significance. In order to ensure the validity of an epidemiologic study, all attempts should be made to control confounding. While bias usually occurs in the study design and data collection phases of an epidemiologic study, confounding usually occurs during the design and analysis phases. Epidemiologists can work to control confounding in the design phase by restricting subjects to only certain characteristics, matching to attempt to create study and comparison groups that are similar with respect to potential confounders, and randomization to decrease confounding by increasing the likelihood that the study group is similar to the comparison group with regard to known factors, as well as unknown potential confounders.

### *E. Precision*

Precision is a measure of the amount of nonsystematic or random error that is present in the study. Random error is variability in a measure that is simply due to chance, and it represents unexplained error in a study. In epidemiologic studies, a precise result would be very easily replicated. Random errors tend to cause inconsistency between different studies and may make it less likely that investigators will find an association between exposure and outcome.

### *F. Random Error*

Random error affects the precision (and thus, the accuracy) of an epidemiologic study. Measurement error and sampling variation are the two main components of random error. Measurement error occurs because of an error in the measuring of the value of a variable. This may be the result of inaccurate measuring devices or due to the subjective type of some exposures or outcomes. Measurement error can be minimized by taking multiple measurements for a certain exposure or outcome. For instance, assume the above case-control study designed to investigate the effect of sugary drinks on blood pressure.

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[11] *Id.*

[12] *Id.*

[13] Rosenblatt et al., *Characteristics of women who use perineal powders*. (1998) 92(5) Obstet Gynecol 753.

Investigators might consider taking several measures of blood pressure and using the average to minimize measurement error. A second form of random error, sampling variation, can occur because samples used in an epidemiologic study are only estimates of the desired population of interest to study. Consider again the above case-control study in which investigators report the odds ratio of 1.35 as the risk estimate of the effect of sugary drinks on high blood pressure. Suppose the investigators replicated the study using a new sample of the same size and found that the odds ratio was now 1.8. Assuming systematic errors were controlled for in study design, data collection and analysis, this difference can be explained by random error/sampling variation. A third sample might reveal an odds ratio of 1.1 or 2.5, which demonstrates that sampling variation is both unpredictable and not reproducible. In general, epidemiologists try to reduce sampling variation by increasing sample size. The stronger the relationship between the exposure and outcome, the smaller the group of patients that need to be studied for this relationship to be apparent. If the group being studied is too small, then the causal relationship may be missed, or spurious results may show up by sampling variation and random error.

## V. STUDY DESIGN CONSIDERATIONS

The purpose of epidemiology is to establish associations between exposures and outcomes that may uncover clues to causation. Epidemiologists can explore the relationship between exposure and outcome in humans in real-world situations by observing (observational study designs) or intervening to a limited extent (experimental study designs), as opposed to controlling all aspects of an experiment in the laboratory. Epidemiologists may also gather data from many studies, either observational or experimental (meta-analysis study designs) and summarize the information in an attempt to demonstrate associations between exposure and outcome. As such, there are many different study designs in epidemiologic research in humans, each with strengths and weaknesses.

### *A. Case Reports And Case Series*

Individual level observations can be documented in a case report, a particular clinical situation involving one unique patient, or in a case series, a description of a group of patients with similar clinical findings or conditions. Case reports and case series are helpful tools in generating hypotheses about associations between exposures and outcomes. However, the lack of a comparison group and the likely presence of bias and confounding limit validity, and therefore limit the ability of these types of epidemiologic descriptions to establish causal associations between exposure and outcome.

### *B. Cross-Sectional Studies*

A common epidemiologic study design used in the initial attempts to evaluate associations between exposures and outcomes is the cross-sectional study. In this type of study, both the exposure and outcome are evaluated simultaneously in each study participant. This approach is sometimes referred to as a prevalence study, as cases of disease or outcome identified are prevalent cases of the outcome being investigated. It is impossible to determine the temporality between exposure and outcome with this epidemiologic study design because of the temporal bias that may exist if the disease causes the exposure. For instance, prevalent cases of asthma may be less likely to own a cat than those without asthma. As patients with asthma may have been instructed to not own a cat,

this relationship might lead investigators to conclude that cat ownership is protective against asthma, leading to a phenomenon known as reverse causality. In addition to temporal bias, selection bias due to survivorship may also be present in cross-sectional studies. This may result if exposure in cases leads to shortened survival than those cases who are unexposed. Similar to case-reports and case-series, cross-sectional studies are often used to generate hypotheses about potential causal associations between exposure and outcome.

### *C. Case-Control Studies*

Another common study design used to evaluate the effect of an exposure on an outcome is known as a case-control study. In this type of epidemiologic study, cases are defined as those with a particular outcome and non-cases or controls are defined as those without a certain outcome. Exposure is then retrospectively evaluated and compared between the cases and controls. Thus, in a case-control study, the prevalence of the exposure of interest should be higher among those with the outcome (cases) than those without the outcome (controls). In general, case-control studies provide more information on the temporal relationship between exposure and outcome than cross-sectional studies. However, case-control studies remain susceptible to other forms of bias. Selection bias can occur in a case-control study when the relationship between exposure and outcome differs systematically between the study population and the source population. Because of this, selection bias can sometimes lead to an association when one does not actually exist. Recall bias is common in case-control studies and results from the cases or subjects with disease having a tendency to remember past exposures more than controls. As mentioned above, it may also arise if cases are more likely to investigate possible factors that may increase the risk of developing a certain disease. Recall bias is often less likely to occur when both cases and controls are patients, for example, in hospitalized patients[14] as compared to population-based case-control studies where the degree of thinking about a possible exposure or outcome is likely to be at similar levels.

### *D. Cohort Studies*

A cohort design assigns an individual as either exposed or unexposed and then that individual is followed over time to see if a particular outcome of interest develops. In general, there are two main types of cohort studies – prospective and retrospective. A prospective cohort design establishes exposure status in the beginning of a study and potentially repeatedly during the study, and then the outcome status for each individual is determined during a follow-up period that extends into the future. In a retrospective cohort design, the exposure and outcome have already occurred (as in the use of administrative or registry data), and the exposure status of each individual is determined from a time period that existed in the past with the outcome then being determined during a time period after exposure that may extend to the present. Temporality is established whether a cohort study is prospective or retrospective in design because the exposure status is always determined prior to evaluating outcome status. In general, cohort studies provide more evidence for a causal relationship between exposure and outcome, and can often study many exposure-outcome relationships with less chance for bias and confounding than case-control studies if

[14] Oleckno (2008) at 207; Infante-Rivard, *Hospital or Population Controls for Case-Control Studies of Sever Childhood Diseases?* (2003) 157(2) Am J Epidemiol 176.

the design, conduct, data collection and analysis are properly performed. However, cohort study designs also remain susceptible to certain types of bias and confounding, are often very expensive, take a long time to conduct and may be difficult to perform, especially if the outcome of interest is rare.

### *E. Experimental Studies*

Unlike an observational study, where exposure is not under the control of the investigator, an experimental study is one in which the exposure (intervention) is controlled directly by the investigator. One such experimental study design – the randomized-controlled clinical trial – is a planned epidemiologic experiment where subjects are randomly assigned to an exposure (intervention) or control group to evaluate the effect of the exposure on outcome. Randomized controlled clinical trials are considered the gold standard of epidemiologic studies. Although there are many advantages to an experimental study design, experimental studies are still subject to the effects of bias and confounding if not designed and conducted properly, and there are instances when this design is not suitable to evaluate the causal association between exposure and outcome because of potential for harm, lack of equipoise or ethical concerns.

### *F. Meta-Analysis*

Epidemiologists may use multiple studies that address the same research question to provide an overall statistical summary of the results. This process is known as meta-analysis and is useful when individual studies tend to be inconclusive because of small sample size. A meta-analysis can provide a precise estimate of the effect of an exposure on an outcome of interest by combining the results of relevant studies by using a systematic approach and analysis. Meta-analyses can also help to provide consensus about the effectiveness of interventions, as well as insight or explanation for differences in individual trial results. Meta-analysis is a type of systematic review that utilizes a comprehensive, rigorous and standardized approach to selecting, assessing and synthesizing all relevant studies on a given topic. Systematic reviews that summarize studies without combining the results statistically are often called qualitative systematic reviews, while those that also combine study results statistically to produce an overall summary effect are referred to as quantitative systematic reviews, and are synonymous with meta-analyses. There are fundamental steps that must be followed to ensure the quality of a meta-analysis. These include (a) defining the research question, (b) defining the criteria for study selection, (c) structuring a review of the literature for all eligible studies, (d) structuring data abstraction, (e) reviewing the methods and results of each study critically, (f) summarizing the results of each study using a standard format, (g) using proper statistical tests to provide a summary effect, (h) assessing variation (heterogeneity) between studies and (i) reviewing, interpreting and reporting the findings.[15]

The idea of a meta-analysis is to combine the results of individual studies so that a summary point estimate can be reached that describes the strength of association between exposure and outcome. There are different approaches to modelling data between studies, and it is important to understand that these approaches may produce different results. Fixed-effects models assume that the effect of exposure on outcome is equal in all studies

[15] Oleckno (2008).

included in the meta-analysis, while random-effects models assume that the effect of exposure on outcome varies between each included study due to both actual differences in effect and random error. In general, when the findings of the included studies are similar, both models yield similar summary estimates, but when the findings of the included studies vary appreciably, the models may produce conflicting results. A statistical test of heterogeneity is oftentimes performed to evaluate whether differing results from the included studies are due to chance alone. If unlikely due to chance, then a random effects model may be more appropriate.

It is also important to understand that in addition to the great deal of preparation and structured organization that is involved in conducting a meta-analysis, it is of utmost importance to vigilantly examine the accuracy of the included individual studies when relying on meta-analyses. Many of plaintiffs' epidemiologists, for instance, premise their causation opinions in large part on the various meta-analyses assessing the effect of exposure to talc on ovarian cancer.[16] But, when it comes to concerns over bias and confounding, a pooled analysis or a meta-analysis will only be as good as the included studies. And while some of plaintiffs' experts have performed their own meta-analyses, the underlying limitations of the included studies are not lessened or removed simply by performing additional meta-analyses using the same studies with different groupings.

## VI. EPIDEMIOLOGIC STUDIES OF TALC POWDER AND OVARIAN CANCER

In order to understand the relationship between talc exposure and ovarian cancer, I have performed a search of the peer-reviewed literature. I identified 44 individual studies investigating the exposure/outcome relationship between talcum powder use and ovarian cancer. The individual studies were evaluated with attention to study design, accuracy, exposure assessment, analysis and validity, while noting both strengths and weaknesses.

### *A. Summary Of Article Study Designs*

Due to the exposure (talc powder) and outcome (ovarian cancer) being studied, there were no experimental studies, as this study design would not be suitable to evaluate this relationship. The studies identified can be separated into three categories: (1) case-control studies, (2) cohort studies, and (3) meta-analyses. I reviewed 33 case-control studies (two of which pooled data from different studies), four cohort studies, and seven meta-analyses published between 1982 and 2018.[17]

The 33 case-control studies ranged in size from 123 to 4,092 participants. There were seven hospital-based case-control studies and 26 population-based case-control studies that I reviewed. The assessment of exposure varied extensively in the case-control studies and was obtained from responses to questionnaires on the use of talc, diaphragm with talc, diaphragm storage only, all over body talc, genital talc, legs only talc, not genital talc, talcum powder in the perineum, talcum powder on sanitary pads, talcum powder on

[16] Clarke-Pearson Rep. 7; McTiernan Report 8, 63; Moorman Rep. 10.

[17] I also briefly reviewed the unpublished Taher meta-analysis cited by several of plaintiffs' experts, and it does not affect my analysis. The association it reports is not materially higher than prior studies, and it agrees with IARC's assessment that a causal relationship is merely "possible" in light of current evidence.

diaphragms, after bathing only, baby powder only, deodorizing powder, dusting powder to the perineum, any dusting powder, talc around the abdomen/ perineum, perineal dusting, genital powder application, genital/rectal talc, powder to genitals, powder to diaphragm, or powder to sanitary napkins. All studies included pathologically confirmed cases or cancer registry cases of ovarian cancer. Analyses varied widely among the case-control studies from no adjustment for potential confounders to adjusting for varying degrees of confounding, including age at first birth, age at last birth, age at menarche, age at menopause, tumor behavior, breast feeding, community-based case-control study, diaphragm use, duration of use, exercise, education, frequency of use, family history of breast and ovarian cancer, histologic type, hospital-based case-control study, hair dye use, hormone replacement therapy, hysterectomy, income, use of medications, menopausal status, sanitary napkin use, number of pregnancies, oral contraceptive use, parity, socioeconomic status, timing of use and tubal ligation.

The four cohort studies I reviewed utilized data from the US Nurses' Health Study (NHS), US Nurses' Health Study II, the Women's Health Initiative Observational Study, and the Sister Study and ranged in size from 41,654 to 108,870 participants. The assessment of exposure was obtained from responses to questionnaires on talc use, talc on the perineum or napkin, powder on the genitals, powder on diaphragm, powder on napkin or talc use in the past 12 months. Analyses varied across the different cohort studies with varying degrees of adjustment for potential confounding, including age, age at last birth, menopause status, age at menopause, race, parity, BMI, activity level, breast feeding, oral contraceptive use, duration of oral contraceptive use, estrogen use, postmenopausal hormone use, duration of hormone replacement therapy, tubal ligation, smoking status and family history of breast or ovarian cancer.

### *B. Case-Control Studies: Hospital-Based*

I identified seven hospital-based case-control studies that have evaluated the potential causative association between talc and ovarian cancer, yielding similar non-statistically significant estimates of risk of ovarian cancer and talc usage.

In 1983, Hartge et al.[18] conducted a hospital-based case-control study of pathologically identified ovarian cancer and frequency matched controls of women in the same hospitals in Washington, DC. Interviews were performed and exposures were categorized as "any" use of talc and "genital" exposure to talc. Among women exposed to "any" talc, the odds ratio of ovarian cancer was not statistically significant at 0.7 (95% CI: 0.4-1.1). Among those who reported talc use on genitals, sanitary napkin or underwear, the odds ratio was not statistically significant at 2.5 (95% CI: 0.7-10.0). The study is limited by small sample size and lack of adjustment for potential confounders.

In 1988, Whittemore et al.[19] similarly completed a hospital-based case-control study of histologically confirmed ovarian cancer cases in pre-menopausal and postmenopausal women between the ages of 18 and 74 with primary epithelial ovarian cancer in Santa Clara County hospitals or at the University of California, San Francisco Medical Center and

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[18] Hartge et al., *Talc and Ovarian Cancer*, (1983) 250 J. Am. Med. Ass'n 1844.

[19] Whittemore et. al., *Personal And Environmental Characteristics Related To Epithelial Ovarian Cancer*, (1988) 128 Am J. Epidemiol 1228.

hospitalized controls. In-person interviews were performed, and to evaluate exposure, subjects were asked about whether they had used talcum powder products on the perineum, sanitary pads and/or diaphragms. Participants who responded were asked about frequency and duration of use. Among women who reported perineum only talc use, the odds ratio was not statistically significant at 1.45 (95% CI: 0.81-2.60) after adjustment for parity and oral contraceptive use. There was no trend in increasing duration of treatment, and the risk of ovarian cancer was not statistically significant with increasing frequency of use.

Booth et al.[20] in 1989 performed a hospital-based case-control study of pathologically identified ovarian cancer in women under 65 years of age from 13 hospitals in London and two in Oxford and hospitalized controls. Subjects were interviewed and exposure was obtained through a questionnaire and frequency of talc use was reported as never, rarely, monthly, weekly or daily talc use. There was no statistically significant increase in risk of ovarian cancer between never and daily reported talc use (OR: 1.3; 95% CI: 0.8-1.9) after adjusting for age and social class. There was no trend of increased risk of ovarian cancer with increased frequency of reported talc use, as those participants who reported weekly use had a higher risk estimate (OR: 2.0; 95% CI: 1.3-3.4) than those who reported daily talc use, and no dose-response relationship with frequency of reported talc use was found among those exposed compared to those unexposed after adjusting for age and social class.

Rosenblatt et al.[21] in 1992 reported a hospital-based case-control study evaluating "fiber exposure" generally (with "fiber" defined as asbestos, talc or fiberglass), including "genital fiber use" specifically, which included an assessment of "method of application" in pathologically confirmed cases of ovarian cancer and hospitalized controls between 1981 and 1985 at the Johns Hopkins Hospital. A questionnaire was administered to participants, both by telephone and in the hospital, which was used to obtain reported exposure to talc and presence and length of applying talcum powder to the genital area. There was no statistically significant increase in risk of ovarian cancer with "genital fiber use" (OR: 1.0; 95% CI: 0.2-4.0) after adjustment for parity, or for exposures from diaphragm use with powder (OR: 3.0; 95% CI: 0.8-10.8) after adjustment for parity and education, or genital bath talc exposure (OR: 1.7; 95% CI: 0.7-3.9) in unadjusted analysis. There was also no statistically significant increase in the risk of ovarian cancer with length of exposure (≥37.4 years vs. <37.4 years) to "genital fiber use" (OR: 2.4; 95% CI: 1.0-5.8) after adjustment for religion.

Tzonou et al.[22] in 1993 conducted a case-control study among hospitalized patients from two hospitals in Athens, Greece with histologically confirmed ovarian cancer and hospital visitor controls. In-hospital questionnaires were administered and exposure was obtained as reported use of talc in the perineal region. Even though the prevalence of talc usage was low, there was no statistically significant association between reported exposure of talc to the perineum and risk of ovarian cancer (OR: 1.05; 95% CI: 0.28-3.98). The

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[20] Booth et al., Risk factors for ovarian cancer: a case-control study. (1989) 60(4) *Br J Cancer.* 592.

[21] Rosenblatt et al., *Mineral Fiber Exposure and the Development of Ovarian Cancer*, (1992) 45 Gynecologic Oncology 20.

[22] Tzonou et al., *Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer*. (1993) 55(3) Int J Cancer. 408.

authors adjusted for age, years of schooling, weight before onset of the disease, age at menarche, menopausal status, age at menopause, parity, age at first birth, tobacco smoking, consumption of alcoholic beverages, consumption of coffee, hair dyeing and analgesics-tranquilizers/hypnotics.

Hartge and Stewart[23] in 1994 reported a case-control study of women diagnosed with pathologically confirmed ovarian cancer in the Washington, DC area between 1978 and 1981. This study analyzed occupational history in women who were diagnosed with ovarian cancer and hospital-based controls. Trained interviewers used a standardized questionnaire that included lifetime job history and exposure to talc on the job. An industrial hygienist conducted an industrial hygiene exposure assessment evaluating each job/industry combination for potential exposure to talc, as well as other potential exposures. The risk of ovarian cancer was not significantly increased for any exposure to talc, regardless of the duration of exposure: <5 years (OR: 0.5; 95% CI: 0.1-1.4), 5-9 years (OR: 0.3; 95% CI: 0.1-1.4), 10+ years (OR: 0.5; 95% CI: 0.2-1.5).

Wong et al.[24] in 1999 reported the results of a hospital-based case-control study in patients with ovarian cancer as determined by the Roswell Park Tumor Registry and hospital-based controls. Exposure was evaluated using a self-administered questionnaire regarding medical history and personal hygiene. There was no statistically significant increased risk of ovarian cancer among participants who ever used talc (OR: 1.13; 95% CI: 0.88-1.44)[25] or among those who used talc on both a sanitary napkin and on the genital or thigh area (OR: 1.1; 95% CI: 0.7-1.7). There was a haphazard non-statistically-significant relationship with duration of talc use over time and risk of ovarian cancer: 1-9 years (OR: 0.9; 95% CI: 0.6-1.5), 10-19 years (OR: 1.4; 95% CI: 0.9-2.2), and ≥20 years (OR: 0.9; 95% CI: 0.6-1.2) after adjustment for parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location and history of tubal ligation or hysterectomy.

### *C. Case-Control Studies: Population-Based*

I identified 26 population-based case-control studies (two from pooled data) that assessed the potential causative association between talc and ovarian cancer, yielding conflicting results.

Cramer et al.[26] in 1982 reported the first epidemiologic case-control study of genital talc use and risk of ovarian cancer. Cases were women diagnosed with ovarian cancer in the Greater Boston area between 1978 and 1981 and identified through pathology logs or tumor boards and confirmed pathologically. Controls were identified through annual

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[23] Hartge & Stewart., *Occupation and ovarian cancer: a case-control study in the Washington, DC, metropolitan area, 1978-1981*. (1994) 36(8) J Occup Med. 924.

[24] Wong et al. *Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study*. (1999) 93 Obstet Gynecol 372.

[25] The Wong paper does not report an odds ratio for ever versus never talc use, but the text of the article contains the information necessary to calculate it. Specifically, the text reports that 221 cases out of 421 total had ever used talc and 311 controls out of 693 total had ever used talc. The calculated odds ratio is 1.13 with a 95% CI of 0.88-1.44 (STATA SE 15.1, StataCorp, College Station, TX).

[26] Cramer et al., *Ovarian cancer and talc: a case-control study*. (1982) 50(2) Cancer 372.

listings of Massachusetts residents and were matched by residence, race and age. Subjects were interviewed in person to evaluate potential exposure to talc through contraceptives, hygiene or surgery. After adjustment for parity and menopausal status, a statistically significant association was found between "any perineal exposure" of talc and risk of ovarian cancer (OR: 1.92; 95% CI: 1.27-2.89).

Harlow and Weiss[27] in 1989 conducted a study of perineal use of powder and the risk of borderline ovarian cancer. Caucasian women aged 20-79 from three counties in Washington State diagnosed as having serous or mucinous borderline ovarian tumor were identified using the Seattle-Puget Sound Cancer Surveillance System during the years 1980 to 1985. Independent pathologic review was performed on 73% of cases. A control group was identified through random digit dialing. Reproductive, sexual and medical history, as well as information on talc exposure, was obtained during an in-person interview. There was no statistically significant increase in risk of borderline ovarian tumors with any perineal exposure to powder (OR: 1.1; 95% CI: 0.7-2.1), baby powder use (OR: 0.8; 95% CI: 0.4-1.9), or unspecified talc use (OR: 1.0; 95% CI: 0.4-2.4) after adjusting for age, parity and use of oral contraceptives. Use of deodorizing powder alone (OR: 3.5; 95% CI: 1.2-28.7) and use of deodorant powder alone or in combined use with another powder (OR: 2.8; 95% CI: 1.1-11.7) were both associated with a statistically significant increase in risk of borderline ovarian tumors after adjusting for age, parity and use of oral contraceptives.

Harlow et al.[28] in 1992 reported a case-control study among women 18 to 76 years of age diagnosed with borderline or malignant epithelial ovarian cancer confirmed pathologically from 10 hospitals in the Boston metropolitan area. Controls were selected from the Massachusetts Town Books. An in-person interview was performed to obtain demographic, occupational and medical history, as well as hygienic practices. Exposure was reported as any genital talc, type of application (sanitary napkin, underwear, partner or application to diaphragm, or dusting powder to the perineum) and brand of application (brand or generic baby powder or deodorizing or other scented powders). Application via dusting to the perineum was associated with a statistically significant risk of ovarian cancer (OR: 1.7; 95% CI: 1.1-2.7) after adjusting for parity, education, marital status, religion, use of sanitary napkins, douching, age and weight. Use of any genital talc was not associated with a statically significant increase in risk of ovarian cancer (OR: 1.5; 95% CI: 1.0-2.1) after adjusting for the same potential confounders. Although there was no statistically significant increase in risk of ovarian cancer with increasing lifetime total applications of talc-containing powders after adjusting for the same potential confounders, there was a statistically significant increase in the risk of ovarian cancer with more than 10,000 total lifetime perineal applications of talc-containing powders in participants with hysterectomy, tubal ligation and use during nonovulatory months (OR: 2.8; 95% CI: 1.4-5.4).

Chen et al.[29] in 1992 conducted a case-control study in China in women with pathologically confirmed cases of epithelial ovarian cancer. Controls were identified from

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[27] Harlow & Weiss, *A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc*. (1989) 130(2) Am J Epidemiol. 390.

[28] Harlow et al., *Perineal exposure to talc and ovarian cancer risk*. (1992) 80(1) Obstet Gynecol. 19.

[29] Chen et al., *Risk factors for epithelial ovarian cancer in Beijing, China*. (1992) 21(1) Int J Epidemiol. 23.

the community using a random selection from a neighborhood committee or village. A questionnaire was developed and administered through face-to-face interviews by trained interviewers. There was no statistically significant association with using dusting powder to the lower abdomen and perineum and risk of ovarian cancer (OR: 3.9; 95% CI: 0.9-10.6) after adjusting for education and parity.

Cramer and Xu[30] in 1995 reported on a case-control study of women in the Greater Boston area diagnosed with ovarian cancer. The study combined women diagnosed with ovarian cancer from area hospitals between 1984 and 1987 and confirmed pathologically with a previous study of women diagnosed between 1978 and 1981. Controls were selected from the general population and matched by age and residence. In an unadjusted analysis, talc use was associated with an increase in risk of ovarian cancer (OR: 1.6; 95% CI: 1.2-2.1).

In 1995, Purdie et al.[31] conducted a case-control study in three Australian states of women diagnosed with ovarian cancer that was confirmed pathologically. Controls were drawn at random from the electoral roll and stratified by age and geographic region. Trained interviewers administered a questionnaire in a face-to-face interview, which included questions about marital status, education, ethnicity, height, weight, smoking history, occupation, medical history and history of talc use. Talc use around the abdomen/perineum was associated with an increased risk of ovarian cancer (OR 1.27; 95% CI: 1.04-1.54) after adjusting for parity.

Green et al.[32] in 1997 performed a case-control study using the study population from the Purdie study. Methods for case and control identification were similar to the Purdie study. Ever douching was associated with a non-significant 60% increase in risk of ovarian cancer. Use of talc in the perineal region was associated with an increased risk of ovarian cancer (OR: 1.3; 95% CI: 1.1-1.6) after adjustment for parity, oral contraceptive use, age, education, body mass index, smoking and family history of ovarian cancer. Even though there was a reported 60% increase in risk of ovarian cancer for those who ever-douched, there were no adjustments in multivariable analyses for douching as a potential confounder.

Shushan et al.[33] in 1996 conducted a case-control study of women aged 36 to 64 years with histologically diagnosed primary invasive or borderline epithelial ovarian cancer. Cases were identified through the Israel Cancer Registry. Controls were identified by telephoning randomly selected numbers within the same area codes as the cases. Cases and controls were interviewed using a questionnaire containing details on medical history and exposures. Exposure to talc was recorded as never-seldom and moderate-a lot talc use. A

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[30] Cramer & Xu, *Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cance*r. (1995) 5 Ann Epidemiol. 310.

[31] Purdie et al., *Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study*. Survey of Women's Health Study Group. (1995) 62(6) Int J Cancer. 678.

[32] Green et al., *Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer*. Survey of Women's Health Study Group. (1997) 71(6) Int J Cancer. 948.

[33] Shushan et al., *Human menopausal gonadotropin and the risk of epithelial ovarian cancer**. (1996) 65(1) Fertil Steril. 13.

larger proportion of cases reported moderate-a lot of talc use when compared with controls (10.5% vs. 5.6%; p=0.04) without adjusting for potential confounders.

Chang and Risch[34] in 1997 reported a case-control study among women diagnosed with histologically confirmed borderline and invasive ovarian cancers in Toronto and southern Ontario. Controls were identified through the Ontario Ministry of Finance and random selection based on geographic residence. A questionnaire was developed and administered in-person, in-home. Exposure to talc was evaluated by reported regular talc use, use of talc/cornstarch combination, talc use with a sanitary napkin, talc use after bathing as well as after bath uses per month, and years of after bath use. Although there was a significant increase in risk of ovarian cancer with any talc exposure (OR: 1.42;; 95% CI: 1.08-1.86), there was no dose-response, and in fact there was a non-statistically significant inverse trend for after bath uses per month: <10 (OR: 1.84; 95% CI: 1.24-2.73), 10-25 (OR: 1.13; 95% CI: 0.74-1.72), >25 (OR: 0.95; 95% CI: 0.61-1.49) and for years of after bath use: : <30 (OR: 1.7; 95% CI: 1.09-2.64), 30-40 (OR: 1.44; 95% CI: 0.96-2.15), >40 (OR: 0.87; 95% CI: 0.54-1.38)) after adjusting for age at time of interview, years of oral contraceptive use, number of full-term pregnancies, average duration of breastfeeding per pregnancy, the occurrence of a tubal ligation or hysterectomy, and having a mother/sister with ovarian or breast carcinoma.

Cook et al.[35] in 1997 conducted a case-control study of women diagnosed with invasive or borderline epithelial ovarian cancer from records of the Cancer Surveillance System of western Washington State from 1986 through 1988. Controls were identified by random digit dialing of a larger control pool for other studies of cancer in women. Information regarding genital powder exposure was collected by in-person interviews. The occurrence of lifetime genital powder application and the exclusive use of types of genital powder application, including perineal dusting, diaphragm storage in powder, powder on sanitary napkins and genital deodorant spray, were collected. Reported exposure also included cumulative lifetime days of use for perineal dusting, cumulative lifetime months for diaphragm storage in powder, cumulative lifetime months for powder on sanitary napkins and cumulative lifetime months for genital deodorant spray. The use of different types of powder, including talcum powder, baby powder, cornstarch, deodorizing powder, bath or body powder and unspecified powder, was also reported. Although there was an increase in risk of ovarian cancer in women who dusted their perineal areas with powder after bathing (OR: 1.8; 95% CI: 1.2-2.9), there was no statically significant increase in risk of ovarian cancer with increasing cumulative lifetime days of any perineal dusting. There was also no statistically significant increase in risk of ovarian cancer with exclusive use of talcum powder (OR: 1.2; 95% CI: 0.6-2.5) or with the use of any talcum powder (OR: 1.6; 95% CI: 0.9-2.8) after adjusting for age.

Godard et al.[36] in 1998 reported a case-control study of women with histologic diagnosis of ovarian cancer through the gynecologic oncology clinics of two large teaching

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[34] Chang & Risch, *Perineal talc exposure and risk of ovarian carcinoma*. (1997) 79(12) Cancer. 2396.

[35] Cook et al., *Perineal powder exposure and the risk of ovarian cancer*. (1997) 145(5) Am J Epidemiol. 459.

[36] Godard et al., *Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study*. (1998) 179(2) Am J Obstet Gynecol. 403.

hospitals in Montreal in 1995 and 1996. Controls were obtained through random digit dialing. A questionnaire was developed and administered either in-person or on the phone to obtain medical history and reported exposure to talc on perineum. Talc on the perineum was not statistically associated with an increase in ovarian cancer (OR: 2.49; 95% CI: 0.94-6.58) after adjusting for age at diagnosis, age at last childbirth, age at menarche, age at last oral contraceptive use, tubal ligation or hysterectomy and alcohol use.

Cramer et al.[37] in 1999 conducted a case-control study of women with newly diagnosed ovarian cancer in eastern Massachusetts or New Hampshire identified through tumor boards and statewide cancer registries with review of pathology reports. Controls were identified through random digit dialing. Participants were interviewed in-person using a standardized questionnaire and asked if they regularly used talc, baby powder, or deodorant powder dusted or sprayed on "feet, arms, or other non-genital areas, to the genital or rectal area, on sanitary napkins, or on underwear" as well as a husband's use of powder in his genital area. "[T]ypes of powder(s) used, applications per month and total years of use were assessed in talc users." Any reported personal genital exposure was associated with increased risk of ovarian cancer (1.60; 95% CI: 1.18-2.15) after adjusting for age, study center, tubal ligation, BMI, parity, oral contraceptive use, or primary relative with breast or ovarian cancer. Risk of ovarian cancer increased and then fell (inverse relationship) with increasing years of talc use and with increasing total applications, although these estimates were not statistically significant.

Ness et al.[38] in 2000 reported a case-control study of women diagnosed with ovarian cancer who were identified from 39 hospitals in the Delaware Valley region. Controls were identified through random digit dialing. Statistically significant associations were observed for the use of talc on the feet, etc. (OR: 1.4; 95% CI: 1.1-1.6), the genital/rectal area (OR: 1.5; 95% CI: 1.1-2.0), sanitary napkins (OR: 1.6; 95% CI: 1.1-2.3) and underwear (OR: 1.7; 95% CI: 1.2-2.4) after adjusting for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy and breast-feeding. Risk of ovarian cancer increased and then fell (inverse relationship) with increasing years of talc use and with increasing total applications, although these estimates were not statistically significant.

Mills et al.[39] in 2004 reported a case-control study of epithelial ovarian cancer in 22 counties of Central California and identified cases through two regional cancer registries as women diagnosed with pathologically confirmed epithelial ovarian cancer from 2000 through 2001. Controls were women 18 years or older selected by random digit dialing. All cases and controls were interviewed by telephone to obtain information on history of adult use of talcum powder in the genital area, calendar year(s) of use, frequency of use, and total duration of use. Although there was a statistically significant increase in risk of ovarian cancer with ever talc use (OR: 1.37; 95% CI: 1.02-1.85) after adjusting for age, race/ethnicity, duration of oral contraceptive use and breast feeding, there was no clear

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[37] Cramer et al., *Genital talc exposure and risk of ovarian cancer*. (1999) 81(3) Int J Cancer. 351.

[38] Ness et al., *Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer.* (2000) 11(2) Epidemiology 111.

[39] Mills et al., *Perineal Talc Exposure and Epithelial Ovarian Cancer Risk in the Central Valley of California*. (2004) 112 Int'l J. Cancer 458.

dose-response with relation to frequency and duration of talc use and risk of ovarian cancer after adjusting for the same potential confounders. There was a haphazard relationship between reported frequency of use and risk of ovarian cancer, with estimates increasing with rare to several time a month use, then decreasing with 1-3 times per week, and finally increasing with 4-7 times per week. Similarly, there was a haphazard relationship between duration of use and risk of ovarian cancer, as estimates increased at 4-12 years, then decreased at 13-30 years and decreased further at >30 years reported exposure.

Pike et al.[40] in 2004 conducted a case-control study of women in Los Angeles County with histologically confirmed ovarian cancer or borderline tumors identified by the Cancer Surveillance Program between 18 and 74 years of age from 1992 to 1998. Controls were identified using a systematic algorithm based on the address of the patient. Participants were interviewed in person using a questionnaire covering medical and personal lifestyle history. Genital area talc usage was associated with a statistically significant increase in risk of ovarian cancer (OR: 1.60; 95% CI: 1.18-2.18) after adjustment for ethnicity, age, education, family history of ovarian cancer, tubal ligation, BMI, parity, age at last childbirth, number of births, number of incomplete pregnancies, oral contraceptive use, menopausal status, age at menopause and estrogen-progesterone therapy.

Jordan et al.[41] in 2007 reported a case-control study of women aged 18-79 years with histologically confirmed invasive and borderline ovarian cancer in Australia identified by the Australian Ovarian Cancer Study and state-based cancer registries between 2002 and 2005. Women with benign mucinous tumors were also identified by the Australian Ovarian Cancer Study and through records from three major pathology laboratories. Controls were randomly selected from the Australian Electoral Roll after stratifying for age and state. Participants were asked to complete and return a health and lifestyle questionnaire. Neither moderate talc use in the perineal region (OR: 0.4; 95% CI: 0.1-2.0) nor substantial talc use in the perineal region (OR: 1.0; 95% CI: 0.4-2.1) was associated with a statistically significant increase in risk of invasive mucinous ovarian cancer after adjustment for age, education level, parity, use of oral contraceptives, hysterectomy, tubal ligation and smoking status.

Gates et al.[42] in 2008 reported a nested case-control study of talc use, variants in the GSTM1, GSTT1 and NAT2 genes, and the risk of ovarian cancer using cases from the New England Case-Control Study (NECC) and the Nurses' Health Study (NHS). The "NECC questionnaires included multiple questions about regular use of talcum, baby or deodorizing powder as an adult. Specific questions were asked about type of use (as a dusting powder to the genital area, sanitary napkins, underwear or non-genital areas), frequency of use, age at first use, number of years used and brand of powder used. The 1982 NHS questionnaire requested information on whether the participant had ever commonly applied talcum, baby

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[40] Pike et al., *Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study*. (2004) 82(1) Fertil Steril. 186.

[41] Jordan SJ, Green AC, Whiteman DC, Webb PM, Australian Ovarian Cancer Study Group. *Risk factors for benign, borderline and invasive mucinous ovarian tumors: epidemiological evidence of a neoplastic continuum*? (2007) 107(2) Gynecol Oncol 223.

[42] Gates et al., *Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer*. (2008) 17(9) Cancer Epidemiol Biomarkers 2436.

or deodorizing powder to the perineal area (no, <once/week, 1-6 times/week or daily) or to sanitary napkins (yes/no)." There was a statistically significant increase in the risk of ovarian cancer with regular genital talc use in participants from the NECC study (OR: 1.62: 95% CI: 1.26-2.09) but no statistically significant increase in risk of ovarian cancer with regular talc use in the NHS (OR: 1.48; 95% CI: 0.82-2.68). Similarly, there was a statistically significant increase in the risk of ovarian cancer with daily genital talc use in participants from the NECC study (OR: 1.61: 95% CI: 1.18-2.2) but no statistically significant increase in risk of ovarian cancer with regular talc use in the NHS (OR: 1.34; 95% CI: 0.65-2.76). Regular genital talc use was associated with a statistically significant increase in risk of ovarian cancer using the combined study population (OR: 1.36; 95% CI: 1.14-1.63) after adjustment for duration of oral contraceptive use, parity, tubal ligation, BMI and duration of hormone replacement therapy. There was no clear dose-response with regard to frequency of genital talc use, with estimates falling with less than once a week usage and then rising with 1-6 times a week and daily usage.

Merritt et al.[43] in 2008 reported the Australian Ovarian Cancer Study, which was an Australia-wide case-control study of epithelial ovarian cancer. Cases were women diagnosed with invasive or low malignant potential ovarian cancer aged 18 to 79 years between 2002 and 2005. Controls were selected from the Australia Electoral Roll. Study participants filled out a comprehensive health and lifestyle questionnaire. "To determine use of talcum powder in the perineal region, participants were asked whether they had ever used powder or talc in the genital area or on underwear or sanitary pads/diaphragm. They were asked their age at first use and years of talc use in these areas." Ever perineal use of talcum powder was associated with a statistically significant increase in risk of ovarian cancer (OR: 1.17: 95% CI: 1.01-1.36) after adjusting for age, education, parity and oral contraceptive use. However, there was no clear dose-response relationship, with a random shape of the exposure-response curve between perineal use of talcum powder and risk of ovarian cancer as well as the risk of cancer subtypes.

Moorman et al.[44] in 2009 reported a case-control study of epithelial ovarian cancer conducted in a 48-county region of North Carolina between 1999 and 2008. Cases were identified through the North Carolina Cancer Registry and were confirmed histopathologically. Controls were obtained from the same geographic region through random digit dialing. In-person questionnaires were administered, which included questions on medical history and lifestyle factors, including talc ever use. There was no statistically significant increase in risk of ovarian cancer with ever talc use among both white women (OR: 1.04: 95% CI: 0.82-1.33) and African Americans (OR: 1.19: 95% CI: 0.68-2.09) after adjusting for age.

In 2009, Wu et al.[45] conducted a case-control study of residents of Los Angeles County between the ages of 18 and 74 who had histologically confirmed invasive or

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[43] Merritt et al., *Talcum Powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer*. (2008) 122 Int'l J. Cancer 170.

[44] Moorman et al., *Ovarian Cancer Risk Factors in African-American and White Women*. (2009) 170(5) Am J Epidemiol 598.

[45] Wu et al., *Markers of inflammation and risk of ovarian cancer in Los Angeles County*. (2009) 124 Int'l J. Cancer 1409.

borderline ovarian cancer diagnosed from 1998 through 2002. Cases were identified by the Cancer Surveillance Program. Controls were identified using a neighborhood recruitment algorithm. Participants were interviewed using a questionnaire that covered medical, gynecological, reproductive and lifestyle history. To determine use of talcum powder, subjects were asked if they ever used talc at least once per month for six months or more. If the response was positive, participants were asked if "they had ever used talc in nonperineal areas (feet, arms, chest or back), perineal areas, or on underwear or sanitary pads/diaphragm," as well "frequency of use (times per month) and years of talc use." Ever talc use was associated with a statistically significant risk of ovarian cancer (OR: 1.48; 95% CI: 1.15-1.91) as was talc applied to the perineal area (OR: 1.53; 95% CI: 1.13-2.09) after adjusting for race/ethnicity, age, education, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity. A statistically significant increase in risk of ovarian cancer was also seen in those who used talc for more than 20 years and more than 30 times per month (OR: 2.08; 95% CI: 1.34-3.23) and in those who had more than 52,000 talc uses (OR: 1.99; 95% CI: 1.34-2.96).

Rosenblatt et al.[46] in 2011 reported a case-control study of women from a 13-county area of Washington State who were 35 to 74 years old and who were diagnosed with invasive or borderline epithelial ovarian tumor between 2002 and 2005. Cases were identified through the Cancer Surveillance System and controls were selected by random digit dialing. In-person interviews were performed, and obtained information on demographic and lifestyle characteristics, medical history and obstetrical history. For powder use on sanitary napkins and deodorant spray, investigators recorded the total number of months of use. For the use of powder on the perineum after bathing, only intervals of at least one year when powder was usually used was recorded. Women were also asked to report the "types of powder(s) used after bathing, including talcum, baby, cornstarch, deodorant, body/bath, and other or unknown. The extent of exposure to perineal powder after bathing was assessed as lifetime duration of use . . . and as the estimated lifetime number of applications." There was no statistically significant increase in the risk of ovarian cancer for using powder after bathing (OR: 1.27; 95% CI: 0.97-1.66) after adjusting for age, calendar year of diagnosis/reference date, county of residence, number of full-term births and duration of hormonal contraception.

Kurta et al.[47] in 2012 conducted a case-control study using data from the Hormones and Ovarian Cancer Prediction (HOPE) study. Cases were residents of Western Pennsylvania, Eastern Ohio and Western New York State and had histologically confirmed ovarian, peritoneal or fallopian tube cancers diagnosed between 2003 and 2008. Controls were frequency matched and identified through random digit dialing. Trained interviewers collected questionnaire data that included medical history and information about lifestyle. "Perineal talc use was defined as ever using dusting powder or deodorizing spray on the genital or rectal areas, on sanitary napkins, on underwear, or on diaphragms or cervical caps." Perineal talc use was associated with a statistically significant increase in risk of ovarian cancer (OR: 1.40; 95% CI: 1.16-1.69) after adjusting for age and education.

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[46] Rosenblatt et al., *Genital powder exposure and the risk of epithelial ovarian cancer*. (2011) 22 Cancer Causes Control 737.

[47] Kurta et al., *Use of Fertility Drugs and Risk of Ovarian Cancer: Results from a U.S.-Based Case-Control Study*. (2012) 21(8) Cancer Epidemiol Biomarkers Prev. 1282.

Terry et al.[48] in 2013 reported on a pooled analysis of case-control studies using data from the Ovarian Cancer Association Consortium. Investigators used data from eight case-control studies and included 8,525 cases of ovarian, fallopian tube or peritoneal cancer and 9,859 controls. Genital powder use was defined as "any type of powder (talc, baby, deodorizing, cornstarch, or unspecified/unknown) applied directly or indirectly (by application to sanitary pads, tampons, or underwear) to the genital, perineal, or rectal area." Criteria for regular use varied between studies from "ever use" to "one year or longer." "Women who reported both genital and non-genital powder use were classified as genital users." Genital use of powder was associated with a statistically significant increase in risk of ovarian cancer when compared with no powder use (OR: 1.24; 95% CI: 1.15-1.33) after adjusting for age, oral contraceptive use, parity, tubal ligation history, BMI and race/ethnicity.

Wu et al.[49] in 2015 reported a case-control study of women with newly diagnosed histologically confirmed invasive epithelial ovarian cancer identified through the Cancer Surveillance Program. Cases were non-Hispanic white, Hispanic, or African American women aged 18 to 74 diagnosed between 2003 and 2008. In-person interviews were conducted using questionnaires, which included questions on demographics, lifestyle, medical history, family history and genital talc use. Results are based on pooling of four case-control studies in Los Angeles County investigating invasive epithelial ovarian cancer. Genital talc use was associated with a statistically significant increase in risk for invasive ovarian cancer in all study participants (OR: 1.46; 95% CI: 1.27-1.69); non-Hispanic whites (OR: 1.41; 95% CI: 1.21-1.67) and Hispanics (OR: 1.77; 95% CI: 1.20-2.62), but not in African Americans (OR: 1.56; 95% CI: 0.80-3.04). Every five years of talc use was also associated with a statistically significant increase in risk for invasive ovarian cancer in non-Hispanic whites (OR: 1.14; 95% CI: 1.08-1.21) and Hispanics (OR: 1.18; 95% CI: 1.02-1.36), but not in African Americans (OR: 1.15; 95% CI: 0.90-1.47). Estimates were adjusted for menopausal status, age at menarche, hormone therapy use, BMI, income, education, parity, oral contraceptive use, tubal ligation, endometriosis and family history of ovarian cancer.

Schildkraut et al.[50] in 2016 reported a case-control study of women enrolled in the African American Cancer Epidemiology Study from 11 locations in the United States. Cases included African American women aged 20 to 79 with newly diagnosed ovarian cancer. Controls were African American women who were identified through random digit dialing. Participants completed a baseline telephone interview, which includes questions on demographics, medical history and information on lifestyle. "[P]articipants were asked whether they had ever regularly used talc, cornstarch, baby, or deodorizing powders. Participants were considered 'regular users' if they reported using any of these powders at least one time per month for at least six months, and 'never users' if they did not. Regular users were asked about their frequency and duration of use, age at first use, and whether

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[48] Terry et al., *Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls*. (2013) 6(8) Cancer Prev Res 811.

[49] Wu et al., *African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates*. (2015) 24(7) Cancer Epidemiol Biomarkers Prev. 1094 ("Wu 2015").

[50] Schildkraut (2016).

they applied powders to genital areas (including on underwear or sanitary napkins, or on birth control devices like diaphragms) and/or nongenital areas." There was a statistically significant increase in the risk of ovarian cancer with any genital use of powder (OR: 1.44; 95% CI: 1.11-1.86) after adjusting for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of oral contraceptive use, first-degree family history of breast or ovarian cancer and interview year. In addition, as discussed above, when investigators stratified by the interview date, there was no statistically significant association between ovarian cancer and any genital use of body powder if the interview date was before 2014 (OR: 1.19; 95% CI: 0.87-1.63), but if the interview date was after 2014, there was a statistically significant increase in risk of ovarian cancer with any genital use of body powder (OR: 2.91: 95% CI: 1.70-4.97), after adjusting for the same potential confounders.

Cramer et al.[51] in 2016 reported a pooled analysis of case-control studies of women residing in Eastern Massachusetts and New Hampshire diagnosed with ovarian cancer between the ages of 18 and 80 using data from the NHS and several sites from the Ovarian Cancer Association Consortium. Controls were identified through random digit dialing. Participants "were asked whether they 'regularly' or 'at least monthly' applied powder to the genital or rectal area, sanitary napkins or tampons, underwear, or areas other than the genital-rectal area. Additional details included type of powder, age begun, years used, and applications per month. Lifetime exposure was estimated by multiplying frequency of application per month by months used." This was divided by 360 to yield talc-years, which were divided into separate quartiles for dose-response analysis. Any genital powder use was associated with a statistically significant increase in the risk of ovarian cancer (OR: 1.33; 95% CI: 1.16-1.52) after adjusting for reference age, study center and study phase. There was no clear pattern suggesting a dose-response effect, with a random sine wave pattern with increasing risk, then decreasing risk, then increasing risk with total genital talc applications.

### *D. Cohort Studies*

Gertig et al.[52] reported the relationship between perineal talc use and ovarian cancer using participants from the NHS. This is a prospective study of 121,700 registered nurses in the United States who were ages 30-55 years at enrollment in 1976. Talc exposure was not evaluated when the study began, but questions regarding talc exposure were added in 1982. 78,630 women completed the questions regarding talc at baseline and formed the cohort for analysis and were followed for 14 years (1982-1996). There were 307 women who were subsequently diagnosed with ovarian cancer. After adjusting for confounders, no statistically significant association was found with ever talc use, with a relative risk for ovarian cancer of 1.09 (95% CI: 0.86-1.37) when compared to never talc use. Similarly, no statistically significant association was found with daily talc use, with a relative risk of 1.12 (95% CI: 0.82-1.55) when compared with never talc after adjusting for age, parity, duration of oral contraceptive use, BMI, tubal ligation, smoking status and postmenopausal hormone use. There was an increase in risk of invasive serous ovarian cancer, with a relative risk of

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[51] Cramer et al., *The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States*. (2016) 27(3) Epidemiology 334.

[52] Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*. (2000) 92 J. Nat. Cancer Inst. 249.

1.40 (95% CI: 1.02-1.91) among ever talc users when compared to never talc users after adjusting for the same potential confounders.

Gates et al.[53] examined the association between ovarian cancer risk factors and ovarian cancer by histological subtype in the NHS and Nurses' Health Study II (NHSII). This prospective study included 221,866 women who completed baseline and biennial follow-up providing information on lifestyle factors and disease diagnoses. Follow-up was longer than the Gertig study and was 24 years in the NHS (1982-2006) and six years in the NHSII. There were 924 women who subsequently developed ovarian cancer and 721 cases with the histologies of interest (496 serous invasive, 139 endometrioid, 86 mucinous). Information on regular talc use was collected in 1982 and available for NHS participants only (108,870 women). No statistically significant increases in risk were found between talc used greater than once weekly with all epithelial (RR: 1.06; 95% CI: 0.89-1.28), serous invasive (RR: 1.06; 95% CI: 0.84-1.35), endometrioid (RR: 1.06; 95% CI: 0.66-1.69), or mucinous (RR: 1.5; 95%CI: 0.84-2.66) ovarian cancer when compared with less than once weekly talc use after adjusting for age, BMI, activity level, parity, breastfeeding, oral contraceptive use, tubal ligation, age at menopause, estrogen use, menopause status, smoking status and family history of breast or ovarian cancer.

Houghton et al.[54] assessed the perineal powder use and the risk of ovarian cancer prospectively in the Women's Health Initiative observational cohort, which enrolled postmenopausal women aged 50-79 from 40 clinical centers across the United States from 1993 to 1998 through 2012. Participants completed annual questionnaires to obtain information on risk factors and outcomes, including ovarian cancer. Perineal powder was assessed via self-report at baseline by asking participants if they had ever used powder on their private parts (genital areas). Those who answered yes were asked questions regarding duration of use. Participants were also asked about use with diaphragms and sanitary napkins or pads. There were 61,576 women who completed baseline questionnaires and followed for a mean 12.4 years. There were 429 women who subsequently developed ovarian cancer. No statistically significant increase in risk of ovarian cancer between ever powder use on genitals (HR: 1.12; 95% CI: 0.92-1.36) and never powder use on genitals was found after adjusting for age, race, duration of oral contraceptive use, duration of hormone replacement therapy, family history, age at last birth, BMI, smoking status, tubal ligation and parity. There was also no statistically significant increase in risk from duration of use between talc use greater than 10 years (RR: 0.98; 95% CI: 0.75-1.29) or greater than 20 years (RR: 1.10; 95% CI: 0.82-1.48) when compared with never talc use after adjusting for the same potential confounders. Similarly, no statistically significant increase in risk was found for all serous (RR: 1.16; 95% CI: 0.88-1.53), serous invasive (RR: 1.13; 95% CI: 0.84-1.51), mucinous (RR: 1.03; 95% CI: 0.47-2.27), or endometrioid (RR: 1.29; 95% CI: 0.64-2.61) ovarian cancer between ever talc use and never talc use after adjusting for the same potential confounders.

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[53] Gates et al., *Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype.* (2010) 171 Am. J. Epidemiology 45.

[54] Houghton et al., *Perineal Powder Use and Risk of Ovarian Cancer*. (2014) 106(9) J Nat. Cancer Inst.

Gonzalez et al.[55] evaluated the effect of douching and talc use on the risk of ovarian cancer prospectively in the Sister Study, which enrolled women aged 35 to 74 who had never had breast cancer and who had a sister or half-sister diagnosed with breast cancer in the United States and Puerto Rico from 2003 to 2009 through 2014. Participants completed computer-assisted telephone interviews, which included questions about lifestyle factors and health conditions. Participants also completed a self-administered questionnaire about personal products used in the 12 months prior to enrollment, which included questions about frequency of douching as well as talc use, method of talc use, and frequency of talc use. There were 50,884 women who completed questionnaires and, after excluding participants who had bilateral oophorectomies or ovarian cancer before enrollment or who had no follow-up information, 41,654 women were followed for a median of 6.6 years. There was no statistically significant increased risk of ovarian cancer (HR: 0.73; 95% CI: 0.44-1.2) with ever talc use during the 12 months prior to the study when compared with never talc use after adjusting for race, BMI, parity, duration of oral contraceptive use, baseline menopausal status and tubal ligation. There was, however, a statistically significant increase in risk of ovarian cancer (HR: 1.9: 95% CI: 1.2-2.9) with douching/no talc use when compared with neither use as well as an increased risk of ovarian cancer with douching in the past 12 months (HR: 1.8: 95% CI: 1.2-2.8) when compared with never douching after adjustment for the same potential confounders. This study highlights the potential for douching to be a confounder in previous investigations, and all but one study failed to control for the potential confounding effect of douching and risk of ovarian cancer.

### *E. Summary Of Observational Studies*

Evaluating the association between talc use and ovarian cancer in case-control studies poses several challenges that require attention. The assessment of exposure is difficult because it is solely based on self-report. Talc purchasing and use are not documented in the medical records or available in pharmacy records. As there is no reliable method of confirming talc usage, the accuracy and validity of these studies even under perfect circumstances can be dramatically affected by reporting bias. Additionally, the quantification of talc exposure is very difficult and may be impossible to verify accurately. Powders have varying amounts of talc and can be applied by various methods, leading to more or less exposure. There is no standardized dose/amount that is used, and there is no standard quantification method with verification that has been universally employed among the studies in the medical literature. Various studies collected information on the reported use of talc, diaphragm with talc, diaphragm storage only, all over body talc, genital talc, legs only talc, not genital talc, talcum powder in the perineum, talcum powder on sanitary pads, talcum powder on diaphragms, after bathing only, baby powder only, deodorizing powder, dusting powder to the perineum, any dusting powder, talc around the abdomen/ perineum, perineal dusting, genital powder application, genital/rectal talc, powder to genitals, powder to diaphragm, or powder to sanitary napkins. As such, there are no case-control or cohort epidemiologic studies or meta-analyses that have investigated the effect of a standardized amount of talc usage or a standardized method of use to ensure consistency of the assessment of exposure. In addition, only a few epidemiologic studies have found any dose-response relationship between genital talc use and ovarian cancer.

[55] Gonzalez (2016).

Furthermore, as in all case-control studies, recall bias is also of great concern. This arises from the phenomenon that cases are more likely than controls to think about and remember past exposures. Recall bias leads to differential misclassification of exposure and a falsely elevated estimate of risk between talc exposure and ovarian cancer. This is especially important if an exposure such as talc appeared in the news or was discussed in the public arena as having a possible causative association with ovarian cancer. There is evidence to suggest that hospital-based case-control studies are less likely to be subject to recall bias than population-based case-control studies because the degree to which study subjects think about possible past exposure is more similar (given that both cases and controls are being hospitalized).[56]

In general, cohort studies provide more evidence for a causal relationship between exposure and outcome and can often study many exposure-outcome relationships with less chance for bias and confounding than case-control studies if the design, conduct, data collection and analysis are proper. However, cohort study designs also remain susceptible to certain types of bias and confounding, and cohort studies are often very expensive, take a long time to conduct, and may be difficult to perform, especially if the outcome of interest is rare.

Plaintiffs' epidemiologists repeatedly downplay the results of the four relevant cohort studies. Dr. McTiernan, for example, has the opinion that there are a number of "serious limitations" in the cohort studies, including that they were not specifically designed to investigate the relationship between talc use and ovarian cancer, but rather examined a number of different outcomes.[57] This point is irrelevant as cohort studies are designed specifically to have the ability to investigate many exposure-outcome relationships, even if the cohort study was not specifically designed to look at the exposure-outcome relationship of interest. Dr. McTiernan also criticizes the cohort studies on other grounds – that they did not obtain detailed lifetime histories of talcum powder use and therefore could not measure dose-response; that the sample sizes were too small to detect a relative risk like 1.24; and that the latency period of ovarian cancer makes these studies "not likely reflective of risk from exposure to talcum powder products."[58] But as just explained, no type of study in this context can provide an accurate measure of dose-response due to the problems inherent in relying on study participants' subjective assessments regarding the amount of talcum powder they use, and as I elaborate in part VIII.A below, Dr. McTiernan's criticisms with respect to latency and sample size are speculative and wrong. All of this suggests that Dr. McTiernan's criticisms reflect her own bias. While cohort studies also have their own limitations like any other study design, the focused criticism of cohort studies by plaintiffs' epidemiologists, even though they are generally considered more reliable than case-control studies, suggests a biased approach to their analyses.

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[56] Oleckno, *Epidemiology: Concepts and Methods*. (2008) at 207; Infante-Rivard, *Hospital or Population Controls for Case-Control Studies of Sever Childhood Diseases?* (2003) 157(2) Am J Epidemiol 176.

[57] McTiernan Report 46.

[58] *Id.* at 46-47.

### *F. Meta-Analysis*

Gross et al.[59] in 1995 reviewed nine case-control studies (all previously described above) and one cohort study to evaluate the association between talc and ovarian cancer. The authors combined the results of seven studies and found an increase in risk of ovarian cancer (RR: 1.20; 95% CI: 1.01-1.44) with any talc exposure, and combined the results of five studies and, after adjustment, found an increase in risk of ovarian cancer (RR: 1.29; 95% CI: 1.02-1.63). Unfortunately, there is little detail provided regarding the methods used to identify, evaluate and analyze the studies, making the interpretation of this investigation challenging and problematic. In addition, all of the limitations described above with respect to the included case-control studies remain inherent within this investigation.

Huncharek et al.[60] in 2003 evaluated 15 case-control studies (all previously described above) and one cohort study using a predefined technique for literature search, study inclusion and analysis. The study included data from 11,933 subjects and pooling all subjects demonstrated a summary OR of 1.33 (95% CI: 1.16-1.45) for ovarian cancer with being exposed to never versus ever talc, none versus any talc and never versus any talc. Seven studies analyzed together yielded an inverse relationship between duration of exposure and ovarian cancer, with low-exposure groups having a higher risk and high-exposure groups having a lower risk, demonstrating a lack of clear dose-response. Hospital-based case-control studies demonstrated no significant relationship between talc use and risk of ovarian cancer (RR: 1.19; 95% CI: 0.99-1.41), while population-based case-control studies showed an increased risk of ovarian cancer with talc use (RR: 1.38; 95% CI: 1.25-1.52). As mentioned above, the limitations of the previously described case-control studies remain inherent within this review. Furthermore, differences in recall bias between hospital-based and population-based case-control studies provide one possible explanation for differences found between the two different study designs.

Huncharek et al.[61] in 2007 evaluated nine case-control studies (all previously described above) investigating the association between talc via dusting of contraceptive diaphragms and ovarian cancer in 2,281 cases of ovarian cancer and 3,608 controls using a predefined technique for literature search, study inclusion and analysis. Pooling all subjects demonstrated no significant risk of ovarian cancer with being exposed to talc via dusting of contraceptive diaphragms (OR 1.03; 95% CI: 0.80-1.37). One included case-control study did not explicitly provide data on talc use via contraceptive diaphragms, and without data from this study, the resultant OR was 1.12 (95% CI: 0.84-1.48).[62]

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[59] Gross & Berg, *A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer*. (1995) 5(2) J Expo Anal Environ Epidemiol. 181.

[60] Huncharek et al., *Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from Sixteen Observational Studies*. (2003) 23 Anticancer Res. 1955.

[61] Huncharek et al., *Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies*. (2007) 18 Eur J Cancer Prev 422.

[62] Dr. Zambelli-Weiner has criticized the Huncharek studies and did indeed find some errors in them. However, her analysis did not show that any errors materially affected the conclusions of these studies.

Langseth et al.[63] in 2008 reported on a meta-analysis of 20 case-control studies and make reference to one cohort study. Results were separated into 14 population-based case-control studies and six hospital-based case-control studies. The investigators state that the cohort study showed "no association between cosmetic talc use and risk of all subtypes of ovarian cancer combined," although the results were not shown. The hospital-based case-control studies reported a pooled odds ratio of 1.12 (95% CI: 0.92-1.36) and the population-based case-control studies reported a pooled odds ratio of 1.40 (95% CI: 1.29-1.52). The combined OR from all case-control studies using a fixed effects model was 1.35 (95% CI: 1.26-1.46). This meta-analysis reflects some methodological weaknesses, including the fact that there is no report of a literature search strategy and no structured review of the literature for eligible studies.

Berge et al.[64] in 2018 reported on a meta-analysis of 27 studies, which included 24 case-control studies and three cohort studies. The authors reported a "small increased risk" with a summary relative risk of 1.22 (95% CI: 1.13-1.30) for ever talc use and ovarian cancer, but found that the cohort studies did not show an association (RR 1.02 (95% CI: 0.85-1.20)). The investigators demonstrated that given the total number of exposed and unexposed cases of ovarian cancer, the statistical power of the cohort studies to detect a relative risk difference of 1.25 was 0.99, which matched that of the case-control studies, and thus rejected inadequate power as an explanation for the lack of an association between talc exposure and ovarian cancer in the cohort studies and the heterogeneity between study designs. The study found a "weak trend in RR with duration and frequency of genital talc use," but cautioned that this analysis was based on few studies and that the "modest association between both duration and frequency of use of talc may reflect a true relationship, or recall bias or confounding." The authors noted that several aspects of their analysis, including heterogeneity between case-control and cohort studies, did "not support a causal interpretation of the association."

Penninkilampi et al.[65] in 2018 reported on a meta-analysis of 24 case-control studies and three cohort studies. The study reported a summary odds ratio of 1.31 (95% CI: 1.24, 1.39) for any talc use and ovarian cancer, but this association was not present in cohort studies (OR 1.06 (95% CI: 0.90-1.25)). Although the study reported a statistically significant association in the cohort studies for serous invasive ovarian cancer (OR 1.25 (95% CI: 1.01, 1.55)), it excluded the 2010 Gates study from its analysis. The study further found that more than 3,600 lifetime talc applications "were slightly more associated with ovarian cancer than" fewer than 3,600 lifetime applications (odds ratios of 1.42 and 1.32, respectively), but noted that these data came from case-control studies and were therefore "prone to recall bias" (which the study observed could be particularly problematic due to recent media coverage of talc lawsuits). It also observed that the "mechanism by which perineal talc use may increase the risk of ovarian cancer is uncertain," and in particular that use of NSAIDs "is not inversely associated with the incidence of ovarian cancer, as may be

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[63] Langseth et al., *Perineal use of talc and risk of ovarian cancer*. (2008) 62 J Epidemiol Community Health 358.

[64] Berge et al., *Genital use of talc and risk of ovarian cancer: a meta-analysis*. (2018) 27 Eur J Cancer Prev 248.

[65] Penninkilampi and Eslick, *Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis*. (2018) 29(1) Epidemiology 41.

expected if the etiology was related to chronic inflammation." The authors cited the "substantial need for further research on a potential mechanism" as one reason why a causal relationship could not be established with any certainty.

In summary, the published meta-analyses have been of varying quality and in general observed a weak association (odds ratio roughly 1.3) between talc use and ovarian cancer. However, as the meta-analyses have noted, the observed increased risk is restricted entirely to case-control studies and may be a result of bias and/or confounding. Although different studies employ different techniques to attempt to adjust for these issues, meta-analyses are only as good as their underlying studies, and the fact that the meta-analyses themselves combine studies that used different adjustment approaches can exacerbate issues regarding overall reliability.

## VII. ANALYSIS OF STUDIES

It is my opinion that there is insufficient evidence to support a causal association between exposure to talc and risk of ovarian cancer based on the body of available epidemiologic observational studies that have been performed and reported in the literature. While there is no single method for undertaking a causal assessment based on epidemiology, the criteria formulated by Austin Bradford Hill are often used and are considered the gold standard for evaluating causation once an association has been identified. These include: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimentation and analogy.[66] While Bradford Hill suggests nine different viewpoints to consider in a careful examination of the association between exposure and outcome before concluding that a causal relationship exists, it is important to understand that none of his concepts provide unquestionable evidence for or against a causative relationship and none is required as essential or absolutely necessary. They can simply help to provide a framework to guide epidemiologists to decide whether or not there is another more likely way of explaining the association, including non-causal explanations for the results of individual studies. These other explanations can come from bias, confounding and/or random error (as discussed above), can lead to risk estimates that are falsely higher or lower than actual risk and can even lead to conclusions that an exposure causes disease when it does not.

Even before starting such an analysis, however, one should examine whether the epidemiologic literature establishes a true association – the fundamental predicate of a Bradford Hill analysis. As Hill noted in his seminal article setting forth his epidemiologic approach, before evaluating causation, studies must "reveal an association between two variables, ***perfectly clear-cut and beyond what we would care to attribute to the play of chance***." [67] As I discuss further below, this requirement is likely not satisfied here because we are not presented with a "clear cut" association.

A number of the Hill factors further weigh decidedly against a causal finding in this instance. In particular, and as detailed in this section, lack of consistent results among studies, lack of reliable assessment of exposure to talc, lack of a dose-response relationship

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66 Hill, *Environment and disease: association or causation?* (1965) 58 Proc Royal Soc Med. 295.

67 *Id*.

and lack of strength of association all contribute to my opinion that there is a lack of reliable evidence to conclude that exposure to talc increases the risk of ovarian cancer.

### *A. Lack Of Consistency Between Studies*

One of the most striking aspects of the studies is their inconsistency.

Some studies demonstrate an association between talc use and ovarian cancer, while others do not. As set forth in the table below, there are seven hospital-based case-control studies that consistently demonstrate no statistically significant association between exposure to talc and risk of ovarian cancer. There are four cohort studies that also consistently demonstrate no statistically significant association between exposure to talc and risk of ovarian cancer. There are 26 population-based case-control studies that demonstrate inconsistent results, with some studies demonstrating a statistically significant association between exposure to talc and risk of ovarian cancer, while others demonstrate no statistically significant association between exposure to talc and risk of ovarian cancer. This lack of consistency in finding a statistically significant association between talc use and risk of ovarian cancer likely arises from several factors. The studies use varying questionnaires, describe varying self-reported assessments of talc exposure and varying self-reported assessments of frequency and duration of talc use, and apply no adjustment or varying levels of adjustment for potential confounders. Finally, each one of these observational studies has limitations (recall bias and confounding in case-control studies; lack of repeated measure of exposure in cohort studies). The consistency of effect between hospital-based case-control studies and the cohort studies is somewhat assuring and the heterogeneity among population-based case-control studies weigh against finding a causal relationship between exposure and outcome. In addition, even though the methods for at least two of the reported meta-analyses were relatively robust, the studies that were used in all of the meta-analyses were of limited quality.

### *B. Lack Of Reliable Assessment Of Talc Exposure*

In all of the studies investigating the possible causal association between talc and ovarian cancer, assessment of talc exposure relies on self-report. Talc use is not documented in a medical record or in a pharmacy record in order to confirm, or at least verify, self-reported use. This has a substantial potential to lead to recall and reporting bias, in particular in case-control studies, although this type of bias may also be present in cohort studies. Furthermore, self-reported exposures were obtained from responses to questionnaires on the use of talc or talc products, including: use of talc, diaphragm with talc, diaphragm storage only, all over body talc, genital talc, legs only talc, non-genital talc, talcum powder in the perineum, talcum powder on sanitary pads, talcum powder on diaphragms, “genital fiber use”, after bathing only, baby powder only, deodorizing powder, dusting powder to the perineum, any dusting powder, talc around the abdomen/ perineum, perineal dusting, genital powder application, genital/rectal talc, powder to genitals, powder to diaphragm, or powder to sanitary napkins. Varying amounts of talc exist within different powders, varied methods can be used to apply talc either by spray or by powder, varying amounts may be applied on diaphragms, and the amount applied may be very different depending on the method of application and the person applying it. Questions arise, such as: How much talc is used in dusting? How much talc is used in the perineum? How much

talc is used after bathing only, etc.? In addition, there are no observational studies or meta-analyses that have investigated the effect of a standardized amount of talc usage or a standardized method of use to ensure consistency of the assessment of exposure. As an epidemiologist, I find this lack of ability to quantify a dose to be a gaping hole in the exposure-outcome relationship and a tremendous limitation in all of the epidemiologic studies evaluating talc and risk of ovarian cancer.

### *C. Lack Of A Dose-Response To Talc Exposure*

There have been very few case-control studies and no cohort studies that have reported a dose-response relationship between talc exposure and risk of ovarian cancer; and measures of dose-response generally have varied widely among studies.

Dose-response curves may increase with increasing exposure (i.e., increased risk of heart disease with increasing level of cholesterol) and decrease with increasing exposure (i.e., decreased risk of heart disease with increased doses of cholesterol lowering agent). Typically, a dose-response curve that depicts an increased risk would demonstrate increasing risk with increasing quantity of exposure, increasing frequency of exposure, increasing duration of exposure or a combination. When the curve is concave, convex or has a haphazard random shape, that is a red flag to epidemiologists. Studies that have evaluated the potential for dose-response have found: (1) random or "sine wave" (up and down) risk[68]; (2) convex (up then down) risk[69]; (3) concave (down then up) risk[70]; and (4) even decreasing risk[71] with either increasing frequency or duration of talc use. Studies by Wu[72] and Cramer[73] demonstrated increasing risk of ovarian cancer with increasing frequency and duration of reported talc use, but not all cut-offs were statistically significant. Only one study[74] demonstrated a statistically significant association between duration of reported talc use (per five years of reported genital talc use) and risk of ovarian cancer in Hispanics (OR: 1.18; 95% CI: 1.02-1.36) and non-Hispanic whites (OR: 1.14; 95% CI: 1.08-1.21).

In sum, the vast majority of both case-control and cohort studies demonstrate no statistically significant dose-response relationship between talc use and risk of ovarian cancer.

### *D. Lack Of Strength Of Association*

Another indicator of causality is strength of association.

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68 Booth (1989); Wong (1999); Cook (1997); Mills (2004); Merritt (2008); Gertig (2000).

69 Cramer (1999); Chang (1997); Cramer (2016); Rosenblatt (2011); Houghton (2014).

70 Whittemore (1988); Gates (2008).

71 Hartge (1983).

72 Wu (2009).

73 Cramer (2016).

74 Wu (2015).

Relative risk and odds ratios are two measures of strength of association. The higher the relative risk or odds ratio, the greater the likelihood that the relationship is causal. For instance, the International Primary Pulmonary Hypertension Study was a case-control study where cases were defined as patients with pulmonary hypertension without a known reason.[75] Controls were randomly selected from lists of consecutive patients seen by the same general practitioner. Each participant went through a face-to-face interview and was asked about demographics, medical and surgical history as well as medication history. Use of appetite suppressants was associated with a statistically significant increase in risk of pulmonary hypertension (OR: 6.3; 95% CI: 3.0-13.2) after adjusting for systemic hypertension, use of cocaine or intravenous drugs, smoking status, BMI, weight loss behavior, use of thyroid extracts and possible exposure to anorexic agents. The odds ratio in this study was found to be 6.3, and with a relative risk this high it is unlikely that any other factor could be the cause of the association.

The higher the relative risk or odds ratio, the less likely other factors can explain the association. Similarly, for relative risks or odds ratios that are lower, it is important to understand that there may be factors other than the exposure of interest that can explain the association. Rosenblatt (1998)[76] found a statistically significant association between women who had ever douched and those who used powder in the perineal area (OR: 2.9: 95% CI: 1.6-5.1). Gonzalez et al.[77] as described above evaluated the effect of douching and talc use on the risk of ovarian cancer prospectively in the Sister Study. Results demonstrated no statistically significant increased risk of ovarian cancer (HR: 0.73; 95% CI: 0.44-1.2) with ever talc use when compared with never talc use after adjusting for confounders. However, there was a statistically significant increase in risk of ovarian cancer (HR: 1.9: 95% CI: 1.2-2.9) with douching/no talc use when compared with neither use as well as a statistically significant increase in risk of ovarian cancer with douching in the past 12 months (HR: 1.84: 95% CI: 1.2-2.8) when compared with never douching. As previous studies (except for Harlow et al. (1992)) did not account for douching, the relatively weak statistically significant associations could potentially be explained by confounding. One explanation could be that since talc users are more likely to douche and douching appears to increase risk of ovarian cancer, previous studies may not have captured the correct exposure (douching) in the causal pathway and mistakenly concluded talc to be the exposure that increased risk of ovarian cancer instead of douching. Similarly, it is also possible that the relatively weak yet statistically significant associations seen in some of the case-control studies could be explained by other potential confounders that were only considered in some of the studies or that have not yet even been identified.

In summary, based on evidence in the literature and the lack of consistency across studies, the lack of a reliable assessment of actual talc exposure, the lack of a significant dose-response to talc exposure, and a weak strength of association between a poorly characterized exposure to talc and risk of ovarian cancer, it is impossible to conclude that talc exposure increases the risk of ovarian cancer.

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[75] Abenhaim et al., *Appetite-Suppressant Drugs and the Risk of Primary Pulmonary Hypertension*. (1996) 335(9) N Engl J Med 609.

[76] Rosenblatt (1998).

[77] Gonzalez (2016).

| Author | Odds Ratio/Relative Risk/Hazard Ratio | 95% CI | Statistically Significant Association? |
|---|---|---|---|
| **Hospital-based case-control studies** | | | |
| Hartge et al. (1983) | 0.70 | 0.04-1.10 | No |
| Whittemore et al. (1988) | 1.45 | 0.81-2.60 | No |
| Booth et al. (1989) | 1.30 | 0.80-1.90 | No |
| Rosenblatt et al. (1992) | 1.70 | 0.70-3.90 | No |
| Tzonou et al. (1993) | 1.05 | 0.28-3.98 | No |
| Hartge and Stewart (1994) | 0.30 (5-9 years of talc exposure)<br>0.50 (10+ years) | 0.10-1.40<br>0.20-1.50 | No |
| Wong et al. (1999) | 1.13 | 0.88-1.44 | No |
| **Population-based case-control studies** | | | |
| Cramer et al. (1982) | 1.92 | 1.27-2.89 | Weak |
| Harlow and Weiss. (1989) | 1.10 | 0.70-2.10 | No |
| Harlow et al. (1992) | 1.50 | 1.00-2.10 | Weak |
| Chen et al. (1992) | 3.90 | 0.90-10.6 | No |
| Cramer and Xu (1995) | 1.60 | 1.20-2.10 | Weak |
| Purdie et al. (1995) | 1.27 | 1.04-1.54 | Weak |
| Green et al. (1997) | 1.30 | 1.10-1.60 | Weak |
| Shushan et al. (1996) | 1.97 | 1.06-3.66 | Weak |
| Chang and Risch (1997) | 1.42 | 1.08-1.86 | Weak |
| Cook et al. (1997) | 1.60 | 0.90-2.80 | No |
| Godard et al. (1998) | 2.49 | 0.94-6.58 | No |
| Cramer et al. (1999) | 1.60 | 1.18-2.15 | Weak |
| Ness et al. (2000) | 1.50 | 1.10-2.00 | Weak |
| Mills et al. (2004) | 1.37 | 1.02-1.85 | Weak |
| Pike et al. (2004) | 1.60 | 1.18-2.18 | Weak |
| Jordan et al. (2007) | 1.00 | 0.40-2.10 | No |
| Gates et al. (2008) | 1.36 | 1.14-1.63 | Weak |
| Merritt et al. (2008) | 1.17 | 1.01-1.36 | Weak |
| Moorman et al. (2009) | Afr. Am.: 1.19<br><br>Caucasian: 1.04 | Afr. Am: 0.68-2.09<br>Caucasian: 0.82-1.33 | No |
| Wu et al. (2009) | 1.53 | 1.13-2.09 | Weak |
| Rosenblatt. (2011) | 1.27 | 0.97-1.66 | No |
| Kurta et al. (2012) | 1.40 | 1.16-1.69 | Weak |
| Wu et al. (2015) | 1.46 | 1.27-1.69 | Weak |
| Schildkraut et al. (2016) | 1.44 | 1.11-1.86 | Weak |
| **Pooled case-control studies** | | | |
| Terry et al. (2013) | 1.24 | 1.15-1.33 | Weak |

| Author | Odds Ratio/Relative Risk/Hazard Ratio | 95% CI | Statistically Significant Association? |
|---|---|---|---|
| Cramer et al. (2016) | 1.33 | 1.16-1.52 | Weak |
| **Cohort studies** | | | |
| Gertig et al. (2000) | 1.09 | 0.86-1.37 | No |
| Gates et al. (2010) | 1.06 | 0.89-1.28 | No |
| Houghton et al. (2014) | 1.12 | 0.92-1.36 | No |
| Gonzalez et al. (2016) | 0.73 | 0.44-1.20 | No |

## VIII. METHODOLOGICAL FLAWS IN PLAINTIFFS' EXPERTS' EPIDEMIOLOGY-BASED OPINIONS

I was asked to address whether the causation analyses set forth in the expert reports of plaintiffs' epidemiology experts were conducted in a scientifically reliable manner. As set forth below, I have concluded that there are several significant methodological flaws that are prevalent in multiple plaintiffs' experts' reports, rendering their analyses unreliable.

### *A. Disregard For The Hierarchy Of Evidence*

The hierarchy of evidence is well-established within the scientific community.[78] Consistent with that hierarchy, epidemiologists consider meta-analyses of multiple randomized clinical trials, followed by individual randomized clinical trials, as the strongest evidence to support a causal relationship between an exposure and an outcome. These are followed by the observational designs, with cohort studies, case-control studies, and cross-sectional studies in descending order also providing potential evidence for a causal association between exposure and outcome. The lowest quality of evidence comes from case reports, case series and other descriptive studies. As a general rule, lower-quality studies provide less information on whether a causal relationship exists than studies of higher quality.

Although this hierarchy should not be indiscriminately applied to all research questions and studies, an epidemiologist should provide sound scientific justifications for departing from these well-established norms. For example, a poorly designed and conducted meta-analysis or randomized clinical trial may provide less evidence than a well-designed and conducted cohort or case-control study.

A number of plaintiffs' epidemiologists ignore the well-established hierarchy of evidence in their reviews of the relevant human studies, either by treating all studies equally or, even more troublingly, placing an inappropriate amount of weight on case-control studies that they claim demonstrate a weak association between talc use and ovarian cancer, while ignoring stronger, better designed cohort studies that do not show any association and also better capture the temporal nature that must exist to demonstrate a causal relationship

[78] Nat. Health & Medical Res. Council, *NHMRC Levels of Evidence and Grades for Recommendations for Developers of Clinical Practice Guidelines* (2009).

between exposure and outcome. For example, Dr. Moorman states the following in her report:

> As I evaluated individual epidemiologic studies (case-control and cohort studies) that described the risk for ovarian cancer associated with talc use, I did not weight one design more heavily than the other because there are advantages and disadvantages to each design for evaluating talc as a cause of ovarian cancer.[79]

Likewise, Dr. McTiernan states in her report that "all" studies provide evidence of causal effect.[80] When asked at her deposition about the hierarchy of scientific evidence, Dr. McTiernan testified that she was "not sure what hierarchy" the questioner was referring to and that, in any event, "depending on the question, one type of study could be preferable to another, but in general all of the studies provide information, and we look at the totality of evidence."[81] When I teach students about study design in epidemiology, this is exactly what I tell them ***not*** to do. When evaluating whether causality can be demonstrated from a particular study or series of studies, it is essential to evaluate the strengths and potential weaknesses of each individual study. Because case-control studies are more easily subject to biases and confounding factors and can often not fully capture the temporal relationship between exposure and outcome, as discussed in detail below, they are often less reliable than cohort studies.

Even more problematic than treating all studies the same is plaintiffs' experts' tendency to place ***more*** emphasis on case-control studies than higher-quality cohort studies, despite their limitations. For example, despite her disclaimer of adherence to any hierarchy of evidence, Dr. McTiernan does apply a hierarchy of her own, suggesting that case-control studies are preferable in situations where an exposure is "very difficult to measure and which can change over time."[82] While I agree with her that case-control studies are often "easier" when an exposure may be "difficult to measure,"[83] a poor-quality case-control study does not provide higher quality data due to limitations in design. Furthermore, case-control studies, as mentioned above, can be subject to bias and confounding, even when they are well designed. Even though case-control studies sometimes may be "easier" to conduct, the temporal relationship between exposure and outcome is often more difficult to establish because ascertainment of the exposure is done after the outcome. Finally, it is often extremely difficult for a case-control study design to accurately investigate an exposure that changes over time and a cohort design will more likely be able to investigate time varying exposures than a case-control study design. Dr. McTiernan's suggestion therefore is illogical, and in my opinion, is not supported by any science.

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79 Moorman Report 10.

80 McTiernan Report 18.

81 McTiernan Deposition 118.

82 McTiernan Deposition 117.

83 *Id*.

Dr. McTiernan has also criticized the multiple cohort studies finding no association between talc use and ovarian cancer on the ground that those studies involved an "insufficient number of cases . . . to find a statistically significant result."[84] Dr. McTiernan's criticism seems to be that, because ovarian cancer has a low incidence rate – and so few study participants developed the disease in both the study and control populations – the studies cannot rule out the possibility of a link between talc use and ovarian cancer. This position is incorrect.

The first problem with Dr. McTiernan's criticism is that her focus on the low overall incidence of ovarian cancer in the population is misplaced. Incidence rates reported by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program are estimated rates for ***all*** women. These rates may change from year to year, and rates may be different for different age groups and races as reported by SEER.[85] Observational studies do not study the population at large, but rather a subset of the population (i.e., study participants). And the incidence of ovarian cancer in the population enrolled in the cohort studies, including Gonzalez (2016) (41,654 women),[86] Houghton (2014) (61,576 women),[87] and Gates (2010)/Gertig (2000) (108,870 women),[88] was higher than in the general population, with 429 cases among 68,435 participants who reported exposure to talc, and 943 cases among 141,345 participants who reported no exposure to talc. It is not surprising that the incidence rates of ovarian cancer in the cohort studies are much higher than the reported rates for all females by the SEER Program because the cohort studies may include women who are in general at higher risk of developing ovarian cancer (i.e., older age, family history of cancer etc.).

A higher incidence of disease in the study population means that the number of participants needed to detect true risk is decreased – i.e., smaller sample sizes can detect the same amount of risk. Thus, because the cohort studies involve women who likely have a higher risk of ovarian cancer than the general population as reported by SEER, the study sample sizes needed to detect a given difference in risk between groups will be smaller. (This is why epidemiologists study higher-risk groups for less-common disease.) Specifically, using the Berge study's meta-analysis of cohort studies,[89] which concluded that combined cohort studies yielded no increased risk of ovarian cancer when comparing participants exposed to talc to participants not exposed to talc (RR: 1.02; 95% CI: 0.85-1.20), I calculated that the incidence of ovarian cancer and the overall number of study participants was sufficient to detect a true risk of ovarian cancer of 1.25 with a power of .99.[90] In other words, there would be a 1% chance of being incorrect and concluding that there is no difference in risk of ovarian cancer between participants exposed and unexposed to talc if there was a true increase in risk of ovarian cancer with talc exposure.

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84 McTiernan Deposition 124.

85 https://seer.cancer.gov/statfacts/html/ovary.html.

86 Gonzalez (2016).

87 Houghton (2014).

88 Gates (2010); Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*. (2000) 92 J. Nat. Cancer Inst. 249.

89 Berge 2018.

90 Calculations performed with STATA SE 15.1, StataCorp, College Station, TX.

Dr. Moorman's power-based criticisms are similarly flawed. She relies on commentary by Narod,[91] who states that "the lack of a significant overall association between ever use of talc and ovarian cancer in the cohort studies may be due to the fact that despite the large size of the cohorts, the studies were not adequately powered to detect a relative risk of approximately 1.2." But this commentary rests on sample size calculations with certain assumptions regarding risk of ovarian cancer, including the same incidence rate issue that undermines Dr. McTiernan's critique. When the actual incidence rate of ovarian cancer in the cohort studies is taken into account, it decreases the study sample size needed to the sample sizes reported in the relevant cohort studies.

Relatedly, the fact that so few participants in Gonzalez (2016),[92] Houghton (2014),[93] and Gates (2010)/Gertig (2000),[94] developed ovarian cancer regardless of their talc exposure does not undermine the validity of these studies. To the contrary, it demonstrates that the risk of developing ovarian cancer is small among the higher-risk populations that were studied, and that talc exposure simply does not increase that risk to a statistically significant degree.

Other plaintiffs' experts have criticized cohort studies on the grounds that they do not sufficiently account for the latency period of ovarian cancer. For example, Dr. Siemiatycki has stated that the "short follow-up periods in cohort studies would be a source of bias."[95] According to Dr. Siemiatycki, because cohort study researchers "collect information about exposure, and then follow [patients] for two years to find out how many of them got cancer, and whether there is a difference between the people who were exposed and the people who are not exposed, well, that would be pretty hopeless because it takes more than two years for cancers to develop and be diagnosed."[96] But this supposed limitation on cohort studies is greatly exaggerated. Houghton (2014) asked about talcum powder use in study participants who had been followed for up to 18 years and found no statistically significant increased risk in ovarian cancer.[97] Gates (2010) added to the Gertig (2000) cohort and followed study participants for up to 24 years and found no statistically significant elevations in risk for talc use for all epithelial ovarian cancers.[98] Similarly, Gonzalez (2016) followed participants with a sister or half-sister with a history of breast cancer for a median 6.5 years and found no association between the use of talc and ovarian cancer.[99] In any event, the women followed in all of these studies presumably did not start

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91 Narod, *Talc and ovarian cancer*. (2016) 141 Gynecol. Oncol. 410. Plaintiffs' experts Drs. Ellen Blair Smith and Judith Wolf place similar reliance on Narod's commentary on the power of cohort studies to detect risk. (Blair Smith Rep. at 20; Wolf Rep. at 6.)

92 Gonzalez (2016).

93 Houghton (2014).

94 Gates (2010); Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*. (2000) 92 J. Nat. Cancer Inst. 249.

95 Siemiatycki Deposition 171.

96 *Id*.

97 Houghton (2014).

98 Gates (2010); Gertig (2000).

99 Gonzalez (2016).

using talc for the first time the day the studies began and therefore would have had longer durations of use than the time period of the study – in most cases many years more.

### *B. Ignoring Or Minimizing The Effects Of Recall Bias And Other Biases In Case-Control Studies*

Recall bias is of particular concern in retrospective case-control studies because, as compared to controls, cases "tend to search their memories to identify what might have caused their disease; healthy controls have no such motivation."[100] This, in turn, tends to artificially increase the supposed effect of the exposure. As Vetter and Mascha point out, a number of factors can affect recall bias.[101] Study participants with a particular disease tend to "search their memories to identify what might have caused their disease," whereas "healthy controls have no such motivation."[102] Cases tend to remember past exposures more than controls, and cases are often more likely than controls to investigate whether certain risk factors increase the risk of developing a certain disease. In addition, individuals with a disease may have greater awareness of potential risk factors for their condition or may have become sensitized by repeated physician interviews. Consider again the previous example of the investigator who is trying to determine if there is a relationship between sugary drinks and high blood pressure. If the cases tend to recall and report more sugary drink consumption simply because they have reflected more on their past experiences, recall bias could result in differential misclassification and a false overestimation of the measure of risk between the sugary drinks and high blood pressure. Because cases and controls have different incentives to recall past exposures, recall bias can lead to finding associations between exposures and diseases that do not exist. As I explained earlier, the Schildkraut case-control study demonstrates an excellent example of the effect of recall bias in assessing the effects of genital talc use before and after the year 2014.
Dr. Singh attempts to minimize this finding because "there was a statistically significant increased risk both before and after 2014."[103] This is incorrect, as there is only a statistically significant association between any genital body powder use and ovarian cancer in interviews conducted after 2014, providing an exceptional real-world example of the possibility of recall bias in a case-control epidemiologic study. Likewise, Dr. McTiernan asserts that recall bias is "unlikely" to be an issue because the studies for which data collection pre-dated news reports of this association showed similar effects to those for which data were collected afterward.[104] However, there is no reason to believe that recall bias did not affect cases reporting perineal talc use before 2014, since there were reports of an association in the medical literature (and presumably, the media) prior to that time – and the tendency in a case-control study for cases to remember past exposures more than controls is an issue that affects case-control studies regardless of date.

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[100] Grimes & Schultz, *Bias and causal associations in observational research*. (2002) 259(9302) Lancet 248.

[101] Vetter & Mascha, *Bias, Confounding, and Interaction: Lions and Tigers, and Bears, Oh My!*. (2017) 125(3) Anesth Analg 1042.

[102] Grimes & Schultz (2002).

[103] Singh Report 45-46.

[104] McTiernan Report 24.

Dr. Siemiatycki also states that if recall bias were present, "we would systematically see elevated RRs from case-control studies for all manner of variables in all kinds of studies."[105] This makes little epidemiologic sense, as recall bias is a known particular concern in retrospective studies that use a case-control design to investigate the association between exposure and outcome.[106]

### *C. Jumping To Causation Without Sufficiently Determining Association*

Epidemiologists and other researchers are often asked to determine whether an exposure can cause an illness. As noted above, the Bradford Hill factors supply the commonly used framework for undertaking such an analysis. But as also noted above, the existence of a clear-cut, statistically significant association is a prerequisite to such an analysis. One needs to find an association between exposure and outcome first, and it is not acceptable epidemiologic methodology to apply the Bradford Hill criteria in the absence of an established association.

Plaintiffs' experts have the opinion that "most" or the "vast majority" of the epidemiological studies show an increased relative risk of ovarian cancer for genital talc users. For example:

- Dr. Moorman states that, "among the more than two dozen studies that have reported on the association between talc use and ovarian cancer, the vast majority of them reported relative risks or odds ratios greater than one[.]"[107]

- Dr. Singh concludes that "[m]ost case control studies demonstrate an increased risk factor of ovarian cancer associated with talc use with an OR between 1.3 and 1.6, even after adjusting for various risk factors."[108]

- Dr. Smith-Bindman pronounces that her "review of case-control studies on talcum powder use and ovarian cancer risk were consistent and indicate a 50% increase in risk of serous invasive cancer related to routine talcum powder exposure compared to no exposure."[109]

The table in Section VII demonstrates that none of the hospital-based case-control studies, none of the cohort studies, and nearly half of the population-based case-control studies found no statistically significant association. Given that the association found in the literature is far from "perfectly clear-cut," it is not clear to me that a Bradford Hill analysis is even appropriate in this situation.

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105 Siemiatycki Report 54.

106 Schultz & Grimes (2002).

107 Moorman Report 15.

108 Singh Report 53.

109 Smith-Bindman Report 34 (emphasis omitted).

### *D. Methodological Problems With Dr. Smith-Bindman's Meta-Analysis*

One of plaintiffs' epidemiologists, Dr. Smith-Bindman, conducted her own, new meta-analysis of a portion of the talc literature for purposes of this litigation. There are significant problems with her approach that render it unreliable. The first is that the rationale for a new non-peer-reviewed meta-analysis – in an area that has already been subject to repeated meta-analyses on substantially the same body of literature – is not clearly stated. "Although this subject has hardly been studied, repeating or updating rarely (9%) leads to changes in the pooled results of meta-analyses."[110] Therefore, while repeated meta-analyses should not be "discouraged a priori," an "important question" is the "rationale for repeating the analysis" and, where the results differ from prior studies, another important question is "how [the] authors defend their conclusions in relation to prior studies."[111] Dr. Smith-Bindman does not adequately do this; nor does she subject this new meta-analysis to any form of peer review – one of the cornerstones of the body of evidence contained in the medical literature. Under a section of her report that is supposed to set forth a "rationale" for her new meta-analysis, she fails to explain the methodological shortcomings of prior meta-analyses.[112] Instead, she asserts that she believes that "the most important research question to answer in this review is whether regular exposure to talcum powder is associated with ovarian cancer" – and serous cancer particularly – and thus that her review should be limited to those studies that supply data for "as close to approximately daily" use of talcum powder as possible.[113] But she does not explain why daily use is the right metric. Nor, in any event, does she actually limit her review to daily use, which, as she acknowledges, is not specifically examined in all of the studies she included in her review; and at the same time, she also excluded studies that did address daily use based on her own (unexplained) assessment that their "research methods were poorly defined."[114]

Dr. Smith-Bindman reports an odds ratio of 1.43 for all ovarian cancers that is somewhat higher than prior meta-analyses,[115] and ultimately that the association is indicative of a causal relationship.[116] She does not explain why these results might be more valid and defensible in relation to prior meta-analyses, which report somewhat lower odds ratios and reach the opposite conclusion on causation. The sum total of her discussion on this is that "[t]he existing systematic reviews (in particular Penninkilampi and Berge) also concluded a significant increase in ovarian cancer risk following talcum powder exposure,"[117] but she fails to acknowledge that the odds ratios were lower and that neither study embraced a causal conclusion in its review of the overall scientific literature. This omission is critical. Scientists do not practice in a vacuum; they must take into account the

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110 Vavken & Dorotka, *A Systematic Review of Conflicting Meta-Analyses in Orthopaedic Surgery*. (2009) 467(10) Clin Orthop Relat Res. 2723.

111 *Id.*

112 Smith-Bindman Report 30.

113 *Id*. at 31.

114 *Id*. at 32.

115 *Id.* at 33.

116 *Id.* at 41.

117 *Id.* at 34.

entire existing body of scientific evidence. Dr. Smith-Bindman's failure to do so in any meaningful sense, as well as her failure to state the fact that there are no studies that investigated a standardized dose of talc, a standardized method of exposure to talc, or a validated assessment of the frequency and duration of talc usage, makes this a pointless exercise. Because of these fundamental flaws in her study, there is no valid basis to accept her unique perspective over the body of work of many other investigators over several decades that has reached the opposite conclusion.

A second problem with Dr. Smith-Bindman's approach concerns her treatment of serous ovarian cancer specifically. Dr. Smith-Bindman claims to have found data concerning serous ovarian cancer specifically from four studies.[118] But such post-hoc analyses are often speculative because identifying subgroups after the fact can be subject to problems associated with confounding. Therefore, while these analyses may be hypothesis-generating, caution is advised in interpreting the results. For instance, if weight, socioeconomic status, race or douching each were causally related to the risk of serous ovarian cancer and also related to the use of talc but were not investigated in the post-hoc analysis because the study was not designed to look at these factors, then investigators may conclude there is an association when one does not in reality exist between talc use and serous ovarian cancer.

Identifying subgroups after the fact is also inherently prone to bias because of the investigator's impressions of the results of the study.[119] Essentially, it allows the researcher to start with a conclusion and work backwards, which is exactly the opposite of the scientific method. And even setting aside the bias concerns in such a backwards endeavor, findings from post-hoc analyses may also be spurious because the study was not designed to address questions that are developed post-hoc, and thus, for example, no effort would have been made to match cases and controls within the subgroup.

Dr. Smith-Bindman's meta-analysis has other methodological flaws as well. For instance, Dr. Smith-Bindman stated that she alone performed "the search, according – obtaining all the papers, and then reviewing the bibliography of all those papers."[120] Most meta-analyses of higher quality involve more than one investigator to perform the search to decide what studies to include and what studies not to include in order to avoid bias. This was not done.[121] She also states that Dr. Hall helped her with "abstracting the data as a second set of eyes and in doing the statistical summary."[122] Based on her deposition, there also appear to be discrepancies between the numbers reported in Dr. Smith-Bindman's meta-analysis and those from the published literature, and she testified that she "was struggling to understand why the numbers and the figures were not exactly the same as the ones . . . in the published manuscript."[123] Dr. Smith-Bindman, as she stated in her

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118 *Id.*

119 Wang et al., *Statistics in Medicine – Reporting of Subgroup Analyses in Clinical Trials*. (2007) 357(21) N Engl J Med 2189.

120 Smith-Bindman Deposition (Vol. I) 101.

121 *Id.*

122 *Id.*

123 Smith-Bindman Deposition (Vol. II) 255-56.

deposition, called Dr. Hall in between the first and second part of her deposition to ask Dr. Hall "to clarify how she did the calculations of the numbers that are shown in the figures."[124] These irregularities further call her meta-analysis into question.

### *E. Methodological Errors In Plaintiffs' Epidemiologists' Bradford Hill Analyses*

Once an association has been established, Bradford Hill set forth a framework to help assess whether a causal relationship exists: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimentation, and analogy. To the extent a Bradford Hill analysis is even called for, plaintiffs' experts took an irregular approach that seems to be results-driven. In my discussion below, I focus on three criteria – strength of association, consistency of association and biologic gradient – that are the most relevant to my opinions and experience as an epidemiologist.

#### *1. Plaintiffs' epidemiologists find a "strong" association where there is none.*

Strength of association measures the level of increased risk of developing a particular disease as a result of exposure to a particular substance. Strength of association is typically measured by calculating an odds ratio or relative risk – i.e., the ratio of the risk of disease in the population exposed to the risk of disease in those unexposed. A relative risk of 1.0 would indicate that there is no difference in disease risk between individuals exposed and those who are not. When the risk is low, epidemiologists typically require other strong evidence of causation.

Although there is no universal numeric definition of a "strong" association between exposure and outcome in terms of risk, it is generally accepted that ratios of risk measures between 1.1 and 2.0 represent a weak association between exposure and outcome in part because other factors (bias, confounding and random error) have the potential to explain away an apparent association of that level. [125] One after another, plaintiffs' epidemiologists mischaracterize the – at best – weak association between talc use and ovarian cancer as one that is strong. For example:

- Dr. Siemiatycki states that "***[such] a high and significant*** [relative risk] could not have occurred by chance."[126]

- Dr. Singh writes that he "place[s] significant weight on the fact that studies demonstrate ***a strong association*** between talcum powder use and ovarian cancer[.]"[127]

- Dr. Moorman concludes that, "[t]aken as a whole, the ***overwhelming statistical strength of these studies***, whose results are replicated over decades across a wide

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[124] *Id.* 255.

[125] Wynder et al., *Radford Conference Report: Weak associations in epidemiology and their interpretation (3rd ed.)*. (1982) 11 Prev. Med. 464.

[126] Siemiatycki Report 63 (emphasis added).

[127] Singh Report 63 (emphasis added).

variety of populations and investigators, further supported by consistent meta-analysis, weighs very heavily in favor of a causal inference."[128]

In his own non-peer-reviewed meta-analysis, Dr. Siemiatycki calculated the relative risk as 1.28. While I agree with Dr. Siemiatycki that a summary relative risk of 1.28, in general, represents that an exposed group has a 28% increased risk of an outcome, a relative risk in this range is weak, and may well result from bias, confounding, and/or random error rather than a true causal relationship. There is simply no disagreement about this within the scientific community. Plaintiffs' experts' insistence that a 1.28 relative risk is "high" raises the concern that they are pursuing a results-driven approach to their causation analysis instead of proper scientific methodology.

Furthermore, Dr. Siemiatycki states that "the statistical significance of individual studies is irrelevant to the consideration of causality; it is the totality of evidence embodied in the meta-analysis that counts."[129] This might be something to consider in an ideal setting where multiple studies exist to evaluate the effect of a certain exposure that had the same design, the same conduct and the same analysis. But in this instance, in evaluating the effect of talc exposure on the risk of ovarian cancer, one cannot simply ignore the results of individual studies by lumping them together, especially when the individual studies were very different in terms of design, conduct, and analysis.

### *2. Plaintiffs' experts fabricate consistency by ignoring inconsistent studies.*

Plaintiffs' experts uniformly assert that the consistency criterion has been satisfied. Dr. Singh states, for example, that "the direction and strength of association of talc and ovarian cancer is generally consistent across studies."[130] Dr. McTiernan likewise concludes that "the association between use of talcum powder products and risk of ovarian cancer was highly consistent."[131] I would agree with plaintiffs' experts that there are some consistencies among the studies, but those consistencies are among hospital-based case-control studies and among large cohort studies showing no statistically significant association between talc exposure and ovarian cancer. By contrast, there are inconsistencies between hospital-based and population-based case-control studies and within population-based case-control studies. As mentioned above, there are seven hospital-based case-control studies that demonstrate no statistically significant association between talc exposure and risk of ovarian cancer, while there are 26 population-based case-control studies that show inconsistent results, with some studies demonstrating a significant effect of talc exposure on risk of ovarian cancer and others showing no significant effect of talc exposure on risk of ovarian cancer. In addition, there are four cohort studies that also demonstrate no statistically significant association between talc exposure and risk of ovarian cancer. This lack of consistency both within and between study designs suggests that any association may result from bias, confounding, and/or random error, and therefore weighs against a causal relationship.

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128 Moorman Report 29 (emphasis added).

129 Siemiatycki Report 63.

130 Singh Report 63.

131 McTiernan Report 64.

Moreover, it is important to remember (contrary to the suggestion of several of plaintiffs' experts) that for this criterion to weigh in favor of finding a causal relationship, there must be a consistency in ***statistically significant*** associations. Consistency in relative risks that are not statistically significant is not meaningful because that sort of consistency does not provide any degree of confidence that the claim of association made by the study is more than random chance.

### *3. Plaintiffs' experts claim there is a dose-response where none exists.*

A causal association is far more likely if there is demonstrated biological gradient – i.e., a dose-response such that a greater dose leads to a greater risk of disease incidence rate. Almost every epidemiological study has failed to show any dose-response relationship between genital talc use and ovarian cancer as described above.[132] Indeed, plaintiffs' own expert Dr. Siemiatycki acknowledged in 2008 that "[t]he main epidemiological evidence against the association [between talc use and ovarian cancer] is the absence of clear exposure-response associations in most studies[.]"[133]

In responding to this scientific consensus, plaintiffs' epidemiologists insist that the literature supports a finding of a dose-response relationship. For example, Dr. Siemiatycki has the opinion that "there is a clear indication of increasing risk with increasing cumulative exposure" in the Terry 2013 and Schildkraut 2016 studies.[134] But the Terry study – which Dr. Siemiatycki calls "the most important piece of evidence we have on dose-response"[135] – "observed no significant trend . . . in risk with increasing number of lifetime applications."[136] A significant trend was found in that study only when non-users were included in the analysis. Including individuals who are not exposed to a substance in calculating a dose-response trend is inappropriate, however, because it renders this criterion redundant of the strength-of-association inquiry. Dr. Siemiatycki dismissed the fact that the p-value for the trend is not statistically significant by suggesting that "the absence of statistical significance of the trend among the four exposed subsets is not equivalent to the demonstration of an absence of dose-response."[137] That is pure speculation; if the trend line cannot be shown to be statistically significant, then there is no way to tell whether an actual relationship exists. The Schildkraut study likewise only included findings on the difference in risk between, in essence, never-users and ever-users of talc, and its analysis is therefore not relevant to a dose-response relationship.

Indeed, determining the dose of talc exposure is problematic. As Dr. Moorman acknowledges, the relevant dose of talc is not the amount applied but the amount, if any,

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132 Nat. Cancer Inst., *Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ) – Health Professional Version*, https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#link/_220_toc (last updated Jan. 4, 2019); Gonzalez (2016); Houghton (2014); Gates (2010).

133 Langseth (2008).

134 Siemiatycki Report 63.

135 *Id.* at 45.

136 Terry (2013).

137 Siemiatycki Report 44.

that actually reaches the ovaries.[138] However, there is no validated method of evaluating the amount applied, let alone how much (if any) reaches the ovaries. As previously discussed, asking a woman how much talc she powdered on to the underwear is not something that can be objectively measured. Instead, it is inherently subjective and prone to inaccurate estimation. As also discussed above, this creates the potential for recall, reporting, and measurement bias, all of which can lead to false conclusions based on the results. For all of these reasons, the potential for inaccurate classification of exposure leads to tremendous limitations in the entire body of relevant literature, limiting the ability to conclude that there is a causal relationship between talc exposure and ovarian cancer.

## IX. SUMMARY AND CONCLUSIONS ASSESSING CAUSALITY

In designing an epidemiological study, the goal of a scientist is to derive findings that represent the truth in the population being studied. In this respect, choosing a study design that minimizes or eliminates the effects of bias and confounding is very important. In the context of assessing whether epidemiological studies indicate an association between genital talc use and ovarian cancer, recall bias is of particular concern among case-control studies and has demonstrably affected findings of association.

The methodologies used by plaintiffs' experts ignore fundamental principles of epidemiology. In particular, plaintiffs' experts ignore the hierarchy of evidence in evaluating studies and rely on study designs that are inherently susceptible to bias. Specifically, plaintiffs' experts pay particular attention to criticizing cohort studies, with little acknowledgment of the limitations in the case-control studies that find weak associations.

Plaintiffs' experts generally agree that even the studies that do show an association between talc use and ovarian cancer have found a relative risk in the range of 1.2-1.6. This, by definition, is a weak association. Plaintiffs' epidemiologists nonetheless characterize the association as "strong." Likewise, plaintiffs' epidemiologists try to demonstrate a dose-response relationship by relying on methodologically flawed studies and statistically insignificant trend lines. They also see consistency where the studies are inherently inconsistent.

As a professor of medicine and of public health, I have focused my career on using the science of epidemiology as a scientific tool to help improve our understanding of health and disease. The distortion of epidemiological science for purposes of litigation does not achieve those goals. Instead, it undermines scientific efforts to better understand the etiology of disease.

When analyzed in a methodological manner, the body of medical literature simply does not support the conclusion that perineal exposure to talc causes ovarian cancer.

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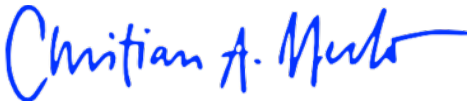
[138] Moorman Report 30.

# APPENDIX A

Curriculum Vitae for Academic Promotion
The Johns Hopkins University School of Medicine



Christian A. Merlo, M.D., M.P.H. February 22, 2019

## DEMOGRAPHIC AND PERSONAL INFORMATION

### Current Appointments

| | |
|---|---|
| 2006-2015 | Assistant Professor of Medicine, Johns Hopkins University School of Medicine |
| 2009-2015 | Assistant Professor of Epidemiology, Johns Hopkins University Bloomberg School of Public Health |
| 2010-present | Associate Program Director for Scholarship, Osler House Staff Program, Johns Hopkins University School of Medicine |
| 2014-present | Director of Outpatient Services, Johns Hopkins Division of Pulmonary and Critical Care Medicine |
| 2015-present | Associate Program Director, Adult Cystic Fibrosis Center, Johns Hopkins Cystic Fibrosis Center |
| 2015-present | Associate Professor of Medicine, Johns Hopkins University School of Medicine |
| 2015-present | Associate Professor of Epidemiology, Johns Hopkins University Bloomberg School of Public Health |

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### Education and Training

Undergraduate

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|---|---|
| 1992 | A.B., Biology/Visual Arts, The College of The Holy Cross, Worcester, MA, *cum laude* |

Doctoral/graduate

| | |
|---|---|
| 1996 | M.D., Georgetown University School of Medicine, Washington, DC |
| 2003 | M.P.H., Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD |

Postdoctoral

| | |
|---|---|
| 1996-1997 | Intern, Internal Medicine, Georgetown University School of Medicine, Washington, DC |
| 1997-1999 | Resident, Internal Medicine, Georgetown University School of Medicine, Washington, DC |
| 1999-2000 | Chief Resident, Internal Medicine, Georgetown University School of Medicine, Washington, DC |
| 2000-2001 | Clinical Fellow, Division of Pulmonary & Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD |
| 2001-2004 | Research Fellow, Division of Pulmonary & Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD |

### Professional Experience:

| | |
|---|---|
| 1999-2000 | Instructor, Georgetown University School of Medicine, Washington, DC |

| | |
|---|---|
| 2003-2004 | Intensivist, Virginia Hospital Center, Arlington, VA |
| 2004-2006 | Instructor, Johns Hopkins University School of Medicine, Baltimore, MD |
| 2006-2015 | Assistant Professor, Johns Hopkins University School of Medicine, Baltimore, MD |
| 2009-2015 | Assistant Professor of Epidemiology, Department of Epidemiology, JHSPH |
| 2015-present | Associate Professor, Johns Hopkins University School of Medicine, Baltimore, MD |
| 2015-present | Associate Professor of Epidemiology, Department of Epidemiology, JHSPH |

**RESEARCH ACTIVITIES**

**Peer Reviewed Original Science Publications**

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65. Magruder JT, Crawford TC, Grimm JC, Kim B, Shah AS, Bush EL, Higgins RS, **Merlo CA**. Risk Factors for De Novo Malignancy Following Lung Transplantation. Am J Transplant. 2017 Jan;17(1):227-238. doi: 10.1111/ajt.13925. Epub 2016 Aug 25. PubMed PMID: 27321167.
66. Magruder JT, Shah AS, Crawford TC, Grimm JC, Kim B, Orens JB, Bush EL, Higgins RS, **Merlo CA**. Simulated Regionalization of Heart and Lung Transplantation in the United States. Am J Transplant. 2017 Feb;17(2):485-495. doi: 10.1111/ajt.13967. Epub 2016 Sep 12. PubMed PMID: 27618731.
67. Drummond MB, Lambert AA, Hussien AF, Lin CT, **Merlo CA**, Wise RA, Kirk GD, Brown RH. HIV Infection Is Independently Associated with Increased CT Scan Lung Density. Acad Radiol. 2017 Feb;24(2):137-145. doi: 10.1016/j.acra.2016.09.019. Epub 2016 Nov 18. PubMed PMID: 27876271; PubMed Central PMCID: PMC5237394.
68. Jennings MT, Dezube R, Paranjape S, West NE, Hong G, Braun A, Grant J, **Merlo CA**, Lechtzin N. An Observational Study of Outcomes and Tolerances in Patients with Cystic Fibrosis Initiated on Lumacaftor/Ivacaftor. Ann Am Thorac Soc. 2017 Apr 13. doi: 10.1513/AnnalsATS.201701-058OC. [Epub ahead of print] PubMed PMID: 28406713.
69. Jennings MT, Dasenbrook EC, Lechtzin N, Boyle MP, **Merlo CA**. Risk factors for persistent methicillin-resistant Staphylococcus aureus infection in cystic fibrosis. J Cyst Fibros. 2017 Apr 23. pii: S1569-1993(17)30106-6. doi: 10.1016/j.jcf.2017.04.010. [Epub ahead of print] PubMed PMID: 28446387.
70. Crawford TC, Grimm JC, Magruder JT, Ha J, Sciortino CM, Kim BS, Bush EL, Conte JV, Higgins RS, Shah AS, **Merlo CA**. Lung Transplant Mortality Is Improving in Recipients With a Lung Allocation Score in the Upper Quartile. Ann Thorac Surg. 2017 May;103(5):1607-1613. doi: 10.1016/j.athoracsur.2016.11.057. Epub 2017 Feb 21. PubMed PMID: 28223052.
71. Crawford TC, Magruder JT, Grimm JC, Suarez-Pierre A, Zhou X, Ha JS, Higgins RS, Broderick SR, Orens JB, Shah P, **Merlo CA**, Kim BS, Bush EL. Impaired Renal Function Should Not Be a Barrier to Transplantation in Patients With Cystic Fibrosis. Ann Thorac Surg. 2017 Aug 16. pii: S0003-4975(17)30707-5. doi: 10.1016/j.athoracsur.2017.05.032. [Epub ahead of print] PubMed PMID: 28822537.
72. Reed RM, Cabral HJ, Dransfield MT, Eberlein M, Merlo CA, Mulligan MJ, Netzer G, Sanchez PG, Scharf SM, Sin DD, Celli BR. Survival of Lung Transplant Candidates With COPD: BODE Score Reconsidered. Chest. 2018 Mar;153(3):697-701.
73. Orens JB, Merlo CA. Selection of Candidates for Lung Transplantation and Controversial Issues. Semin Respir Crit Care Med. 2018 Apr;39(2):117-125.
74. Crawford TC, Lui C, Magruder JT, Ha JS, Higgins RS, Merlo CA, Kim BS, Bush EL. Five-year mortality hazard is reduced in chronic obstructive pulmonary disease patients receiving double- versus single-lung transplants. J Surg Res. 2018 Jun 2.
75. Hong G, Psoter KJ, Jennings MT, Merlo CA, Boyle MP, Hadjiliadis D, Kawut SM, Lechtzin N. Risk factors for persistent Aspergillus respiratory isolation in cystic fibrosis. J Cyst Fibros. 2018 Sep;17(5):624-630.
76. Crawford TC, Lui C, Magruder JT, Suarez-Pierre A, Ha JS, Higgins RS, Broderick SR, Merlo CA, Kim BS, Bush EL. Traumatically Brain-Injured Donors and the Impact on Lung Transplantation Survival. Ann Thorac Surg. 2018 Sep;106(3):842-847.
77. Hsu J, Krishnan A, Lin CT, Shah PD, Broderick SR, Higgins RSD, Merlo CA, Bush EL.Sarcopenia of the Psoas Muscles is Associated with Poor Outcomes Following Lung Transplantation. Ann Thorac Surg. 2018 Nov 14;.
78. Sharma N, Evans TA, Pellicore MJ, Davis E, Aksit MA, McCague AF, Joynt AT, Lu Z, Han ST, Anzmann AF, Lam AN, Thaxton A, West N, Merlo C, Gottschalk LB, Raraigh KS, Sosnay PR, Cotton CU, Cutting GR. Capitalizing on the heterogeneous effects of CFTR nonsense and frameshift variants to inform therapeutic strategy for cystic fibrosis.PLoS Genet. 2018 Nov;14(11):e1007723.

79. Fraser CD 3rd, Zhou X, Grimm JC, Suarez-Pierre A, Crawford TC, Lui C, Bush EL, Hibino N, Jacobs ML, Vricella LA, Merlo C. Size Mismatching Increases Mortality Following Lung Transplantation in Pre-Adolescent Patients. Ann Thorac Surg. 2019 Feb 11;.

**Invited Reviews**

1. **Merlo CA**, Boyle MP. Modifier genes in cystic fibrosis lung disease. J Lab Clin Med 2003;141:237-41.
2. **Merlo CA**, Orens JB. Candidate selection, overall results, and choosing the right operation. Semin Respir Crit Care Med 2010;31:99-107.
3. Braun AT, **Merlo CA**. Cystic fibrosis lung transplantation. Curr Opin Pulm Med 2011;17:467-72.
4. Kirk GD, **Merlo CA**, For the Lung HIV Study Group. HIV infection in the etiology of lung cancer: confounding, causality, and consequences. Proc Am Thorac Soc 2011;8:326-32.
5. Lambert AA, **Merlo CA**, Kirk GD. Human immunodeficiency virus-associated lung malignancies. Clin Chest Med 2013;34:255-72.

**Inventions, Patents, Copyrights**

2010 **Merlo CA**, Reh DR, Hoag JB. Method and severity scale for measuring epistaxis among patients with hereditary hemorrhagic telangiectasia (HHT). Used worldwide as a primary outcome in HHT interventional clinical trials.

**Extramural Sponsorship (current, pending, previous)**

**Current Grants**

09/26/13 – 07/31/18

Immune Mechanisms of HIV-associated COPD
U01HL121814
NIH
$505,539
PI: Gregory Kirk, MD PhD (Johns Hopkins School of Public Health)
Role: Co-I
0.60 calendar months
This proposal directly addresses critical gaps in our understanding of the clinical spectrum and consequences of HIV-associated COPD and will identify key biologic mechanisms contributing to the disease. Findings will inform the clinical management and development of interventions targeting HIV associated COPD, and may also inform broader strategies for COPD in non-HIV infected populations.

07/01/14 – 06/30/19

Clinical Risk Factors for Primary Graft Dysfunction
R01HL087115
NIH subaward
$19,984
PI: Jason Christie, MD (University of Pennsylvania)
Role: Co-I
0.12 calendar months
The major goal of this multicenter study is to define risk factors for the development of primary graft dysfunction following lung transplantation.

09/01/14 – 08/31/18

Predictors, consequences and mechanisms of accelerated lung aging in HIV
R01HL126549
NIH
$499,997
PI: Gregory Kirk, MD PhD (Johns Hopkins School of Public Health)
Role: Co-I
0.60 calendar months
The goal of this program is to establish risk factors, associated co-morbidities, and immunologic and inflammatory biomarkers associated with accelerated decline in lung function in the SHIELD cohort of HIV-positive inner-city intravenous drug users.

07/01/15 – 06/30/18

Transition of Care for Patients with Cystic Fibrosis who Undergo Lung Transplantation
Spruance Foundation II Discovery Fund

$300,000
PI: Christian Merlo, MD MPH
2.4 calendar months
The major goal of this proposal is to identify factors which may help to improve the process of lung transplantation for patients with cystic fibrosis.

**Previous**

07/01/03 – 06/30/04

Gene Expression Analysis of Nasal Respiratory Epithelial Cells in ΔF508/ΔF508 Individuals with Mild and Severe Cystic Fibrosis Lung Disease
Bauernschmidt Fellowship in Pulmonary Disease
Eudowood Foundation
$35000
Role: PI
The goal of this study was to evaluate differences in gene expression between patients with cystic fibrosis with mild and severe lung disease.

07/01/04 – 06/30/07

The Effect of Multiple Antibiotic Resistant *Pseudomonas aeruginosa* on Outcomes in Cystic Fibrosis
The Harry Shwachman Clinical Investigator Award
Cystic Fibrosis Foundation
$270000
Role: PI
6.0 calendar months
The goal of this study was to evaluate the impact of multiple antibiotic resistant *Pseudomonas aeruginosa* (MARPA) on outcomes among patients with cystic fibrosis.

07/01/06 – 06/30/07

Emphysema and HIV infection within the ALIVE cohort in Baltimore
Thomas and Carol McCann Innovative research Fund for Asthma and Respiratory Disease
$35000
Role: Co-PI
The main goal of this study was to evaluate the association between emphysema and HIV infection among the ALIVE cohort in Baltimore.

01/01/08 – 12/30/12

The Study of HIV Infection in the Etiology of Lung Disease (SHIELD)
RFAHL07008
NIH
$549,598
PI: Gregory Kirk, MD PhD (Johns Hopkins School of Public Health)
Role: Co-PI
0.60 calendar months

06/01/11 – 02/28/15

North American Study of Epistaxis in HHT (NOSE)
Hereditary Hemorrhagic Telangiectasia Foundation
$11,126
Role: site PI
0.12 calendar months
This was a multicenter randomized placebo-controlled trial comparing bevacizumab, estrogen, tranexamic acid, and placebo in patients with HHT-related epistaxis.

09/06/12 – 06/30/14

Using mHealth to Respond Early to Acute Exacerbations of COPD in HIV mREACH
R34HL117349
NIH
$376,291
PI: Gregory Kirk, MD PhD (Johns Hopkins School of Public Health)
Role: Co-I
0.60 calendar months

This clinical trial planning grant evaluated the feasibility, acceptability and defined optimal trial elements for an m-Health intervention to identify early exacerbations in HIV-COPD to improve management and clinical outcomes.

**Research Program Building / Leadership:**

2010-present Associate Program Director for Scholarship, Osler Residency Program, Johns Hopkins University School of Medicine. In my capacity, I am responsible for the research experience for the Osler House Staff thoughout residency training. This involves one on one meetings to discuss research interests and goals, an online lecture series providing an introduction to research, pairing with faculty mentors, mentorship in the presentation of research projects at local and national meetings, collecting data highlighting scholarly activity, and reporting these data to the Director for internal use as well as for ACGME purposes.

2010-present Director of Research, The Johns Hopkins Lung Transplant Program. In my capacity, I am responsible for coordination of research efforts within the lung transplant program. This involves multidisciplinary projects spanning across many disciplines (Medicine, Surgery, Rehabilitation, Psychology, Epidemiology) as well as across different levels of training from faculty, fellows, residents, and medical students.

2010-2018 Director, Hereditary Hemorrhagic Telangiectasia Center of Excellence. In my capacity, I am responsible for the coordination of multicenter clinical trials as well as local investigations among patients with HHT. Our center was responsible for creation of an epistaxis severity score (HHT-ESS), the first objective measure of epistaxis severity, now used worldwide clinically as well as an outcome measure in HHT clinical investigations.

2016-present Associate Director, The Johns Hopkins Adult Cystic Fibrosis Program. In my capacity, I am responsible for the coordination of aspects of clinical and research coordination for our cystic fibrosis program.

2016-present Director of Research, The Johns Hopkins Adult Cystic Fibrosis Program. In my capacity, I am responsible for coordination of research efforts within the Adult CF program. This involves multidisciplinary projects spanning across many disciplines (Medicine, Surgery, Psychology, Epidemiology) as well as across different levels of training from faculty, fellows, residents, and medical students.

**EDUCATIONAL ACTIVITIES**

**Educational Publications**

**Peer-reviewed, original, educational publications –** None

**Review Articles –** None

**Editorials –** None

**Case Reports**

1. **Merlo CA**, Studer SM, Conte JV, Yang SC, Sonnett J, Orens JB. The course of neurofibromatosis type 1 on immunosuppression after lung transplantation: report of 2 cases. J Heart Lung Transplant 2004; 23: 774-776.
2. Houston B, Reiss KA, **Merlo C**. Healthy, but comatose. Am J Med 2011; 124: 303-305.

**Book and Book Chapters**

1. **Merlo CA**, Boyle MP. "Adult Cystic Fibrosis". In The Osler Medical Handbook. Mosby. Philadelphia: 60, 899-911, 2003.
2. **Merlo CA**, Terry PB. Concise Review: Diagnosis and management of pulmonary arteriovenous malformations. In Harrison's Online. 2002. http://www.harrisonsonline.com.
3. **Merlo CA**, Hansel N. "Have a working knowledge of EMTALA laws as they apply to the ICU. How to be a good referring and accepting ICU physician". In Avoiding Common ICU Errors. Lippincott. 2008.
4. **Merlo CA**. Critical Care Medicine. In First Aid for the Internal Medicine Boards. McGraw-Hill. New York: 16, 123-132, 2010.

5. **Merlo CA**. Pulmonary Medicine. In First Aid for the Internal Medicine Boards. McGraw-Hill. New York: 4, 553-580, 2010.
6. Dasenbrook EC, **Merlo CA**. "Cystic Fibrosis and Bronchiectasis". In Lung Transplantation. Informa. 2010.
7. Hayes M, **Merlo CA**. "Hemoptysis". The Principles and Practice of Hospital Medicine, 1st Edition, Sylvia C. McKean, Editor-in-Chief, McGraw-Hill publishers.
8. **Merlo CA**. "Diffuse Parenchymal Lung Disease." In Current Therapy in Thoracic and Cardiovascular Surgery. Mosby 2013.
9. **Merlo CA**, Terry PB. "Chest X-Ray Review". In The Johns Hopkins Internal Medical Board Review. Mosby. 2015

**Letters, correspondence** - None

**Other Media -** None

**Teaching**

**Classroom instruction**

| | |
|---|---|
| 2003-2010 | Pulmonary physiology small group facilitator, Johns Hopkins University School of Medicine, Baltimore, MD. |
| 2003-2010 | Pulmonary pathophysiology small group facilitator, Johns Hopkins University School of Medicine, Baltimore, MD. |
| 2004-2010 | Good Samaritan Internal Medicine Program Guest Lectures – Cystic Fibrosis, Pulmonary Function Testing, Baltimore, MD. |
| 2004-present | Lecturer, Carol Johns Service (Inpatient Pulmonary Service) – Lecture monthly about Cystic Fibrosis and Lung Transplantation to medical students, residents, and fellows as part of the core curriculum on the inpatient pulmonary service, Johns Hopkins University School of Medicine, Baltimore, MD. |
| 2004-present | Lecturer, Pulmonary and Critical Care Medicine Fellow's Core Conference – Cystic Fibrosis, Lung Transplantation, Hereditary Hemorrhagic Telangiectasia, and Noninfectious Pulmonary Complications of HIV, Johns Hopkins University School of Medicine, Baltimore, MD. |
| 2006-2014 | Chest Radiography Conference Director – Lecture weekly for 10-15 Pulmonary and Critical Care Medicine fellows regarding the reading of chest radiographs and computed tomography, Johns Hopkins University School of Medicine, Baltimore, MD. |

**Clinical Instruction**

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| 2004-present | Medical Intensive Care Unit. Attending physician 4 to 6 weeks per year, Johns Hopkins. |
| 2004-present | Pulmonary Consultation Service. Attending physician four weeks per year, Johns Hopkins. |
| 2004-present | Lung Transplantation and Pulmonary Hypertension Service. Attending physician 8 weeks per year, Johns Hopkins. |
| 2004-present | Pulmonary Physiology Service. Attending physician four weeks per year, Johns Hopkins. |
| 2005-present | Janeway Firm Faculty. Teaching Attending 4 weeks per year, Johns Hopkins. |

**CME Instruction**

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|---|---|
| 5/06 | PFT interpretation, Topics/Tumulty Rounds, Johns Hopkins, Baltimore, MD. |
| 4/06 | Challenging infections among adults with cystic fibrosis. Medical Grand Rounds. Johns Hopkins, Baltimore, MD |
| 8/07 | Update in Pulmonary and Critical Care Medicine, Johns Hopkins, Williamsburg VA. |
| 1/07 | Cough for the Allergist, Allergy Symposium, Bayview Medical Center, Baltimore, MD. |
| 7/08 | Update in Pulmonary and Critical Care Medicine, Johns Hopkins, Bar Harbor ME. |
| 2/09 | Hereditary Hemorrhagic Telangiectasia- A Fresh Start to an Old Disease. Medical Grand Rounds. Johns Hopkins, Baltimore, MD. |
| 7/09 | Update in Pulmonary and Critical Care Medicine, Johns Hopkins, Washington DC. |
| 1/10 | An update in Cystic Fibrosis, Allergy Lecture Series, Johns Hopkins, Baltimore, MD. |
| 4/12 | Nutritional Considerations after Lung Transplantation in Cystic Fibrosis. Nutrition Grand Rounds. Johns Hopkins, Baltimore, MD. |
| 9/12 | Hereditary Hemorrhagic Telangiectasia. Medical Grand Rounds. Johns Hopkins Bayview. Baltimore, MD. |
| 5/14 | A Curious Case of Hypoxemia, Topics/Tumulty Rounds, Johns Hopkins, Baltimore, MD. |

9/14 Creating a Common Language in Cystic Fibrosis to Improve Adherence, Lecturer, Med-IQ. www.med-iq.com/a796

**Workshops/ Seminars**

5/08 Invited Lecturer, Observational Studies, Short Course in Epidemiology. American Thoracic Society, Toronto, ON.

10/09 Symposium Chairperson, Infectious Complications in Cystic Fibrosis. North American Cystic Fibrosis Conference, Minneapolis MN.

10/10 Symposium Chairperson, End Stage Lung Disease in CF: From Lung transplantation to Paliative Care, North American Cystic Fibrosis Conference, Baltimore, MD.

10/10 Invited Lecturer. Rise and Shine Workshop Management of Hemoptysis and Pneumothorax in Cystic Fibrosis. North American Cystic Fibrosis Conference, Baltimore, MD.

**Mentoring**

Advisees

2006-2010 Elliott Dasenbrook, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine Johns Hopkins University, currently Assistant Professor of Medicine at Case Western Reserve, Cleveland, OH.

2006-2010 Jeffrey Hoag, MD, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Assistant Professor of Medicine at Drexel University, Philadelphia, PA.

2008-2011 Brad Drummond, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Assistant Professor of Medicine, Johns Hopkins University, Baltimore MD.

2008-2012 Natalie West, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Assistant Professor of Medicine at Johns Hopkins University, Baltimore, MD.

2009-2011 Eric Weiss, MD MPH, Master's of Public Health student at Johns Hopkins Bloomberg School of Public Health, currently Assistant Professor of Surgery (adjunct) at Columbia College of Physicians and Surgeons, New York, NY.

2010-2012 Jeremiah Allen, MD, Resident, Johns Hopkins University, currently Attending Cardiac Surgeon, Kaiser Permanente, San Francisco, CA.

2010-present Andrew Braun, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Instructor of Medicine, Johns Hopkins University, Baltimore, MD.

2011-2013 Timothy George, MD, Resident, Johns Hopkins University, currently Resident Surgeon at Johns Hopkins University, Baltimore, MD.

2011-2014 Arman Kilic, MD, Resident, Johns Hopkins University, currently Resident Surgeon, Johns Hopkins University, Baltimore, MD.

2011-present Mark Jennings, MD, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Instructor of Medicine, Johns Hopkins University, Baltimore, MD.

2012-2016 Allison Lambert, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Instructor of Medicine, Johns Hopkins University, Baltimore, MD.

2012-2016 George Arnaoutakis, MD, Resident, Johns Hopkins Universeity, currently Cardiac Surgery Fellow, University of Pennsylvania, Philadelphia, PA.

2014-present Joshua Grimm, MD, Resident, Johns Hopkins University, currently Resident Surgeon, Johns Hopkins University, Baltimore, MD.

2014-present Linda Yin, Medical student, Johns Hopkins University, currently a medical student at Johns Hopkins University, Baltimore, MD.

2015-present Todd Crawford, MD, Resident, Johns Hopkins University, currently Resident Surgeon, Johns Hopkins University, Baltimore, MD.

2015-present Trent Magruder, MD, Resident, Johns Hopkins University, currently Resident Surgeon, Johns Hopkins University, Baltimore, MD.

**Educational Program Building/ Leadership**

2006-present Course Director, Design of Clinical Studies, Johns Hopkins Bloomberg School of Public Health. This is an ongoing course available in the 2nd term each year through the Department of Epidemiology in the School of Public Health. It is part of a series of courses known formally together as the Science of

Clinical Investigation series. Together these courses convey the fundamentals of clinical research. In my capacity as director, I am responsible each year for the syllabus, lectures, homework assignments, and follow-up questions which arise during the 12-week class. The course has expanded over the years starting with a class size of about 6-8 to know over 40 per term and now includes physicians, nurses, administrators, and research coordinators.

2012-present Course Director, Distance Education Design of Clinical Studies, Johns Hopkins Bloomberg School of Public Health. This is a fully online version of the above course available through the Office of Distance Education in the 3rd term. Lectures, assignments, and quizzes are all available online. Live sessions accompany the online media. This course has also expanded from just a few to over 30 students per session.

**Educational Extramural Funding (Current, Pending, Previous) -** None

**CLINICAL ACTIVITIES**

**Certification**

Medical

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|---|---|---|---|
| 1998 | Medical License, Commonwealth of Virginia | 0101057430 | Inactive |
| 1999 | Medical License, District of Columbia | MD31720 | Inactive |
| 2004-present | Medical License, Maryland | D0061725 | Active |

Boards

2000 Diplomate, Internal Medicine, American Board of Internal Medicine
2003 Diplomate, Pulmonary Disease, American Board of Internal Medicine
2005 Diplomate, Critical Care Medicine, American Board of Internal Medicine

**Clinical Responsibilities**

2004-present Medical Intensive Care Unit. Attending physician 4 to 6 weeks per year, JHH.
2004-present Pulmonary Consultation Service. Attending physician four weeks per year, JHH.
2004-present Lung Transplantation and Pulmonary Hypertension Service. Attending physician 8 weeks per year, JHH.
2004-present Pulmonary Physiology Service. Attending physician four weeks per year, JHH.
2004-present Attend in the Adult Cystic Fibrosis Clinic. One half day per week
2009-present Attend in HHT Clinic. One half day per month
2011-present Attend in the Lung Transplantation Clinic. One half day per week

**Clinical Program Building/Leadership**

2010-2018 Director, Johns Hopkins Hereditary Hemorrhagic Telangiectasia Center of Excellence. In my capacity, I am responsible for the coordination of multidisciplinary care for the patients with HHT that we care for at Johns Hopkins. Working in partnership with Sally Mitchell, MD, we created the Johns Hopkins HHT Center of Excellence in 2010, one of 17 such centers in the United States. The center now includes over 35 specialists from 15 Hopkins Departments and Divisions and has increased exponentially in size to include over 400 patients and family members. The team at Hopkins now consists of a nurse coordinator as well as specialists from nearly every division and department within the Hopkins system.

2015-present Associate Program Director, Johns Hopkins Adult Cystic Fibrosis Center. In my capacity, I assist the Program and Center Director in the coordination of care guidelines and the delivery of clinical care in both the inpatient and outpatient settings, assist with coordination of clinical trials, and provide education to medical students, physicians, nurses, respiratory and physical therapists, nutritionists, social workers, patients, and family members regarding the multidisciplinary subspecialty care needed for patients with CF.

**Clinical Extramural Funding (Current, Pending, Previous) -** None

**SYSTEM INNOVATION AND QUALITY IMPROVEMENT ACTIVITIES -** None

## ORGANIZATIONAL ACTIVITIES

**Institutional Administrative Appointments**

2003-2005 Educational Committee, Division of Pulmonary and Critical Care Medicine
2005-present Faculty Recruitment Committee, Division of Pulmonary and Critical Care
2014-present Assistant Director of Outpatient Services, Johns Hopkins Division of Pulmonary and Critical Care Medicine
2015-present Associate Program Director, Adult Cystic Fibrosis Center, Johns Hopkins Cystic Fibrosis Center

**Editorial Activities -** Not Applicable

**Journal Reviewer**

2009-present Chest
2009-present Journal of Heart and Lung Transplant
2009-present Journal of Cystic Fibrosis
2009-present European Respiratory Journal
2009-present American Journal of Transplantation

**Advisory Committees, Review Groups/Study Sections**

2012-present Member, Cystic Fibrosis Foundation Grant review Committee

**Professional Societies**

2004-present Member, American Thoracic Society
2004-present Member, American College of Chest Physicians
2010-present Member, International Society for Heart and Lung Transplant

**Conference Organizer, Session Chair -** Not Applicable

**Consultantships -** Not Applicable

## RECOGNITION

**Awards, Honors**

1999 Clinical Pearls Student Teaching Appreciation Award
1999 The William P. Argy Memorial House Staff Award
2000 Alpha Omega Alpha, Georgetown University
2003 DC Thoracic Society Annual Conference Award
2003 NIH Loan Repayment Program Award for Clinical Research
2005 Janeway Firm Faculty
2005 CHEST Foundation's Young Investigator Award
2005 NIH Loan Repayment Program Award for Clinical Research
2010 Fellows Teaching Award, Johns Hopkins

**Invited Talks**

Local/National/International

2005 Speaker, Medical Grand Rounds. Virginia Hospital Center. "The Care of Adults with Cystic Fibrosis". Arlington, VA
2005 Speaker, Pulmonary Grand Rounds. The University of Pittsburgh. "The influence of environmental and genetic factors on outcomes in cystic fibrosis". Pittsburgh, PA.
2007 Plenary Speaker, International Society for Heart and Lung Transplant. "The effect of the Lung Allocation Score (LAS) on survival after lung transplantation". San Francisco, CA.
2008 Speaker, North American Cystic Fibrosis Conference. "The Impact of the LAS on Outcomes in CF". Orlando, FL.
2008 Speaker, Mid Atlantic Thoracic Society Conference. "Adult Cystic Fibrosis". Richmond, VA.
2009 Speaker, Hereditary Hemorrhagic Telangiectasia International Scientific Conference. "Quality of Life among Patients with Hereditary Hemorrhagic Telangiectasia". Santander, Spain.
2010 Speaker/ Session Chair, Society for General Internal Medicine. "Research During Residency- Striking the Balance at Hopkins". Minneapolis, MN.

2010 Speaker/ Session Chair, North American Cystic Fibrosis Conference. "Lung Transplantation and Cystic Fibrosis". Baltimore, MD.
2010 Speaker, Pulmonary Grand Rounds. Brown University. "Hereditary Hemorrhagic Telangiectasia". Providence, RI.
2010 Speaker, 8th International Congress on Lung Transplantation. "Understanding and Dissecting the Lung Allocation Scoring System". Paris, France.
2012 Speaker, Medical Grand Rounds. Georgetown University Hospital. "Adult Cystic Fibrosis". Washington, DC.
2012 Speaker, 16th Annual HHT Patient and Family Day, HHT Foundation, "Understanding Screening for HHT." Orlando, FL.
2013 Speaker, American Thoracic Society. "Understanding and Dissecting the Lung Allocation Scoring System". Philadelphia, PA.
2013 Speaker, Cystic Fibrosis Conference Mexico. "Outcomes in Adults with Cystic Fibrosis". Mexico City, Mexico.
2013 Speaker, Hereditary Hemorrhagic Telangiectasia International Scientific Conference. "Minimal Clinical Important Difference in Epistaxis Severity Score in HHT". Cork, Ireland.
2014 Speaker, Medical Grand Rounds. Virginia Hospital Center. "Adult Cystic Fibrosis". Arlington, VA.

**OTHER PROFESSIONAL ACCOMPLISHMENTS**

2013 Washington Post. When should you start worrying about that lingering cough? Give it time. http://www.washingtonpost.com/national/health-science/when-should-you-start-worrying-about-that-lingering-cough-give-it-time/2013/12/20/1e615e9c-665d-11e3-ae56-22de072140a2_story.html
2013 Hopkins Medicine. For Lung Transplant, Researchers Surprised to Learn Bigger Appears to Be Better. http://www.hopkinsmedicine.org/news/media/releases/for_lung_transplant_researchers_surprised_to_learn_bigger_appears_to_be_better_
2014 Cover photograph entitled "A View of the Dome". Annals of the American Thoracic Society, Volume 11, Issue 5. http://www.atsjournals.org/toc/annalsats/11/5
2014 Johns Hopkins Health. Calming that cough. http://www.hopkinsmedicine.org/news/publications/johns_hopkins_health/fall_2014/calming_that_cough
2015 EurekAlert! Lung transplant patients in the UK fare better than publicly insured Americans. http://www.eurekalert.org/pub_releases/2015-03/jhm-ltp031915.php

# APPENDIX B

# APPENDIX B

List of Literature Review and Materials Considered by Dr. Christian Merlo


1. Abenhaim et al., *Appetite-Suppressant Drugs and the Risk of Primary Pulmonary Hypertension.* (1996) 335(9) N Engl J Med 609
2. Berge et al., *Genital use of talc and risk of ovarian cancer: a meta-analysis.* (2018) 27 Eur J Cancer Prev 248
3. Booth et al., *Risk factors for ovarian cancer: a case-control study.* (1989) 60(4) Br J Cancer. 592
4. Centers for Disease Control & Prevention, Principles of Epidemiology in Public Health Practice, Third Edition, An Introduction to Applied Epidemiology and Biostatistics, Lesson 1: Introduction to Epidemiology, https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section1.html
5. Chang & Risch,. *Perineal talc exposure and risk of ovarian carcinoma.* (1997) 79(12) Cancer. 2396
6. Chen et al., *Risk factors for epithelial ovarian cancer in Beijing, China.* (1992) 21(1) Int J Epidemiol. 23
7. Cook et al., *Perineal powder exposure and the risk of ovarian cancer.* (1997) 145(5) Am J Epidemiol. 459
8. Cramer & Xu, *Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer.* (1995) 5 Ann Epidemiol. 310
9. Cramer et al., *Ovarian cancer and talc: a case-control study.* (1982) 50(2) Cancer 372
10. Cramer et al., *The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States.* (2016) 27(3) Epidemiology 334
11. Cramer et al., *Genital talc exposure and risk of ovarian cancer.* (1999) 81(3) Int J Cancer. 351
12. Deposition of Anne McTiernan, M.D., Ph.D., Jan. 28, 2019 (MDL No. 2738)
13. Deposition of April Zambelli-Weiner, Ph.D., Jan. 11, 2019 (MDL No. 2738)
14. Deposition of April Zambelli-Weiner, Ph.D., Feb. 7, 2019 (MDL No. 2738)
15. Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738)
16. Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738)
17. Deposition of Jack Siemiatycki, Jan. 31, 2019 (MDL No. 2738)
18. Deposition of Rebecca Smith-Bindman, M.D., Feb. 7, 2019 (MDL No. 2738)
19. Deposition of Rebecca Smith-Bindman, M.D., Feb. 8, 2019 (MDL No. 2738)
20. Deposition of Patricia Moorman, M.S.P.H., Ph.D., Jan. 25, 2019 (MDL No. 2738)
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24. Expert Report of April Zambelli-Weiner, Ph.D., M.P.H., Nov. 16, 2018 (MDL No. 2738)
25. Expert Report of Ghassan Saed, Ph.D., Nov. 16, 2018 (MDL No. 2738)
26. Expert Report of Jack Siemiatycki, M.Sc., Ph.D., Nov. 16, 2018 (MDL No. 2738)
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# APPENDIX C

**Fed. R. Civ. P. 26(a)(2)(B)(v) Disclosure for Christian Merlo, M.D., M.P.H.**

| Year | Parties | State | Caption |
|---|---|---|---|
| 2015 | Blevins v. Pyron | Missouri | Blevins v. Pyron<br>Lawrence County Circuit Court<br>14LW-CC00108 |
| 2015 | Grove v. UMMS | Maryland | Grove v. UMMS<br>USDC Maryland<br>12-cv-2950 |
| 2015 | Dutton v. UMMS | Maryland | Dutton v. UMMS<br>Baltimore City Circuit Court<br>24-C-14-003848 |
| 2015 | Hawkins v. Mercy Kansas | Missouri | Hawkins v. Mercy Kansas<br>St. Louis City Circuit Court<br>1422-CC09810 |
| 2015 | Whitehead v. CVS | Florida | Whitehead v. CVS<br>Miami-Dade County Circuit Court<br>14-25980CA01 |
| 2016 | Evans v. Livingston Health Care | Montana | Evans v. Livingston Health Care<br>Gallatin County District Court<br>DV-11-990B |
| 2016 | Moore v. Mercy | Maryland | Moore v. Mercy<br>Baltimore City Circuit Court<br>24-C-16-004483 |
| 2016 | Quintanilla v. Narayanan | Maryland | Quintanilla v Narayanan<br>Montgomery County Circuit Court<br>397252V |
| 2017 | Burns v. Bowser | Virginia | Burns v. Bowser<br>Virginia 13th Judicial Circuit<br>CL14005484-00 |
| 2017 | Monroe v. Franklin Square | Maryland | Monroe v. Franklin Square<br>Baltimore County Circuit Court<br>03-C-16-001886 |
| 2017 | Weisman v. Maryland General | Maryland | Weisman v. Maryland General<br>Baltimore City Circuit Court<br>24-C-16-004199 |
| 2017 | Almquist v. Kinsey | Maryland | Almquist v. Kinsey<br>USDC Maryland<br>1:15cv292 |
| 2017 | Sullivan v. Holy Cross | Maryland | Sullivan v. Holy Cross<br>Montgomery County Circuit Court<br>423516v |
| 2018 | Flores v. Kaiser | Maryland | Flores v. Kaiser<br>Montgomery County Circuit Court<br>427661v |
| 2018 | Hamlin-Lewis v. Guckes | Maryland | Hamlin-Lewis v. Guckes<br>USDC Maryland<br>1:16cv3357 |
| 2018 | Hirschenson v. Cleveland Clinic | Florida | Hirschenson v. Cleveland Clinic<br>Broward County Circuit Court<br>CACE13001180 |
| 2018 | Knoerlein v. Express Primary Care | Maryland | Knoerlein v. Express Primary Care<br>Baltimore County Circuit Court<br>03-C-17-001137 |
| 2018 | McRae v. Dimensions Health | Maryland | McRae v. Dimensions Health<br>Prince George's County Circuit Court<br>CAL1702184 |
| 2018 | Fluoroquinolone Liability Litigation | New Jersey | |
| 2019 | Jones v. Agrawal | Maryland | Jones vs Bon Secours Hospital Baltimore, Inc, et al ("Jones v. Agrawal")<br>Baltimore County Circuit Court<br>24C18000398 |